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Table of Contents.

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The Halford Oration.[1]

MEDICAL MEN AND BOOKS.

By KEITH INGLIS.

AT the outset let me express my appreciation of the honour that has been conferred on me by the invitation to deliver the Halford Oration for 1939. It is especially gratifying to me because it gives to one who has worked as student and teacher in the medical school of the University of Sydney for over thirty years an opportunity of offering felicitations to the University of Melbourne, in whose medical school George Britton Halford worked as the first professor.

Dr. Halford arrived in Australia in 1862 and took up his duties as professor of anatomy, physiology and pathology. He had already won renown by his experiments on the action of the heart and the causes of its sounds, and had proved himself a successful teacher of anatomy. Others have spoken of his outstanding success in building up the Melbourne medical school, and it occurred to me that it would not be amiss if I chose for my address tonight a subject bearing on Professor Halford's interest in literature. We are reminded of this interest by Dr. W. E. L. H. Crowther, who in the 1934 oration tells us of the last scene at Professor Halford's home at Inverloch. His nurse wrote to Dr. Crowther and said: "Here he passed his days amidst flowers, music and, most beloved of all, his library, with Sir Walter Scott's 'Ivanhoe' never far from his side."

I am the more inclined to choose a subject with a literary trend because I fear that nowadays we who teach or practise medicine share the prevailing

[1] Delivered on November 27, 1939, at the Australian Institute of Anatomy, Canberra.

tendency to stress the importance of utilitarian considerations and to neglect the humanities.

A few years ago a prominent British surgeon visited this country; while in Sydney he looked over a new institute of pathology and we spared no effort in our endeavours to make an impression on him by demonstrating the modern facilities and equipment that had been provided. After the tour of inspection was over our visitor discussed general topics with us, and during this conversation he spoke of his interest in a scholarship for medical students in the Old Country; one of the conditions of this scholarship was that the student holding it had to possess some knowledge of, or acquaintance with, Greek.

That conversation made a great impression on us, for it was in keeping with the reputation that is enjoyed by the medical men of Britain for literary distinction even in scientific contributions; this tradition dates back to Thomas Linacre, that great medical humanist of the early sixteenth century.

Professionalism and Humanism.

In 1917 Professor (later Sir) Mungo MacCallum gave an address to the Sydney University Medical Society on "Professionalism and Humanism". This excellent address was published in the society's journal, and was especially welcome at a time when the thoughts of many medical men on military service were concentrated on professionalism in a very special field. It was consoling and comforting to have the importance of humanism so engagingly presented. Professor MacCallum said that by professionalism he meant devotion to one's vocation, whatever that happened to be—disinterested zeal for one's profession as such, so that one wished to be as good in it as one could possibly be; and by humanism he meant interest in all that pertained to us as men, and especially in what pertained to us peculiarly as men and did not pertain to the lower animals—the preparation of the mind that would enable it to appreciate all the general concerns of human beings, but more distinctively such as appealed not to the physical but to the spiritual side of their nature.

Concerning the dangers of professionalism, Professor MacCallum said that the doctor, dealing with the body and its functions, its behaviour in health and disease, was perhaps more likely to have his field of vision restricted, and restricted to material relations, than the professional men who were concerned with the human mind—and the products of the human mind—in law and institutions, in art and history, in philosophy and religion. He quoted Chaucer, who said of his doctor of physic: "His study was but little on his Bible"; and added that that trait was perhaps typical, even if we enlarged the scope of it. The doctor has little inducement springing immediately from his work to occupy himself with spiritual questions—"spiritual" being used in the widest and most secular sense.

One of the means of combating the dangers of professionalism is to indulge in a course of general reading, and Professor MacCallum, in his plan for reading, gives an important place to his beloved Shakespeare.

The Art of Reading.

Sir Arthur Quiller-Couch, in his introductory lecture on "The Art of Reading", states that Sir Thomas Elyot wrote in the sixteenth century: "Inconveniences always doe happen by ingurgitation and excessive feeding"; and Sir Arthur gives the comments on this statement made by an old schoolmaster and a poet, Mr. James Rhoades, late of Sherborne, which are as follows:

> This is no less true of the mind than of the body. I do not know that a well-informed man, as such, is more worthy than a well-fed one. The brain, indeed, is a nobler organ than the stomach, but on that very account is the less to be excused for indulging in repletion. The temptation I confess is the greater, because for the brain the banquet stands ever spread before our eyes, and is, unhappily, as indestructible as the widow's meal and oil.
>
> Only think what would become of us if the physical food, by which our bodies subsist, instead of being consumed by the eater, was passed on intact by every generation to the next with the superadded hoards of all the ages, the earth's productive power meanwhile increasing year by year beneath the unflagging hand of Science, till, as Comus says, she
>
> . . . would be quite surcharged with her own weight
> And strangled with her waste fertility.
>
> Should we rather not pull down our barns, and build smaller, and make bonfires of what they would not hold? And yet, with regard to Knowledge, the very opposite of this is what we do. We store the whole religiously, . . . And then we put a fearful pressure on ourselves and others to gorge of it as much as ever we can hold. . . . The real tragedy of the Library at Alexandria was not that the incendiaries burned immensely, but that they had neither the leisure nor the taste to discriminate. . . . I believe, if the truth were known, men would be astonished at the small amount of learning with which a high degree of culture is compatible.

Discrimination in the choice of books to be read there must be, and this choice will depend on the taste of the individual. The manner of reading must also vary, for, as Francis Bacon says in his essay "Of Studies":

> Some books are to be tasted, others to be swallowed, and some few to be chewed and digested; that is some books are to be read only in parts; others to be read, but not curiously; and some few to be read wholly, and with diligence and attention.

A. C. Benson, in his essay on "Books" tells us that there used to be a story in his days at Cambridge of a book-collecting don who was fond of discoursing in public of the various crosses he had to bear. He was lamenting one day in Hall the unwieldy size of his library. "I really don't know what to do with my books", he said, and looked round for sympathy. "Why not read them?" said a sharp and caustic fellow opposite. Benson goes on to tell us that there are indeed many books in his college library; but most of them, as D. G. Rossetti used to say in his childhood of his father's learned volumes, are "no good for reading".

Rossetti's father, however, may have held similar views to Montaigne, who, in his essay on "Men, Women and Books", says of his own books:

I make as little use of them in a manner as those who know them not. I enjoy them as misers do their hoards, by knowing that I have them to use as I please. . . . Sometimes for several days or months, I do not look into them. I will read by and by, I say to myself, or tomorrow when I am in the humour.

The Art of Writing.

In discussing books let me direct attention not only to the art of reading, but also to the art of writing. Scientists in general are apt nowadays to pay more heed to the substance of their thesis than to the literary form of its presentation, and purists have at times been so offended by the results as to describe such verbal descriptions as laboratory jargon. In this regard I should like to draw attention to an amusing criticism by Quiller-Couch in his book on "The Art of Writing". After referring to the time when all scientific works were written in Latin, he proceeds:

But when it became an accepted custom for each nation to use its own language in scientific treatises, it certainly was not foreseen that men of science would soon be making discoveries at a rate which left their skill in words out-stripped; that having to invent their terms as they went along, yet being careless and contemptuous of a science in which they have no training, they would bombast out our dictionaries with monstrously invented words that not only would have made Quintilian stare and gasp, but would affront the decently literary of any age.

After all, and though we must sigh and acquiesce in the building of Babel, we have some right to examine the bricks.

After reading these strictures a writer of scientific treatises might well feel humble; but his sense of contrition would weigh less heavily upon him when he continued to read, for Quiller-Couch goes on:

I was waiting the other day, in a doctors' anteroom, and picked up one of those books—it was a work on pathology—so thoughtfully left lying in such places; to persuade us, no doubt, to fear ills we have rather than fly to others capable of being illustrated. I found myself engaged in following the manœuvres of certain well-meaning bacilli generically described as "Antibodies". I do not accuse the author (who seemed to be a learned man) of having invented this abominable term: apparently it passed current among physiologists and he had accepted it for honest coin. I found it, later on, in Webster's invaluable dictionary: Etymology, "anti", up against, "body", some noxious "foreign body" inside your body or mine.

Now gin a body meet a body for our protection and in this gallant spirit, need a body reward him with this hybrid label?

This very entertaining description is based on the false premise that a bacillus is an antibody. Even an average fourth-year medical student would be expected to know that, in this regard, antibodies are formed by the tissues when they are invaded by the bacilli; the bacillus is not the antibody, it is the antigen. After all, though form of presentation is important in a scientific thesis, accuracy is the first essential.

Study of Old Masters as a Stimulus to Originality.

The opinion is widely held that time devoted to the study of past ages, though interesting, is unprofitable; but even regarded from a purely practical point of view, this opinion is open to question. Quiller-Couch, in his book on "The Art of Writing", refers to the "Discourses" addressed by Sir Joshua Reynolds to the members and students of the Royal Academy. In his second discourse Sir Joshua Reynolds said:

I flatter myself that from the long experience I have had, and the unceasing assiduity with which I have pursued these studies in which like you I have been engaged, I shall be acquitted of vanity in offering some hints to your consideration. They are indeed in a great degree founded upon my own mistakes in the same pursuit.

He then spoke of the old masters and proceeded:

The more extensive, therefore, your acquaintance is with the works of those who have excelled, the more extensive will be your powers of invention—and what may appear still more of a paradox, the more original will be your conceptions.

Sir Edmund Gosse held somewhat similar views on originality; but he went further. In his little book "Father and Son", so delightful, though tinged with sadness, he made this statement:

The rage for what is called "originality" is pushed to such a length in these days that even children are not considered promising, unless they attempt things preposterous and unparalleled. From his earliest hour, the ambitious person is told that to make a road where none has walked before, to do easily what is impossible for others to do at all, to create new forms of thought and expression, are the only recipes for genius; and in trying to escape on all sides from every resemblance to his predecessors, he adopts at once an air of eccentricity and pretentiousness. This continues to be the accepted view of originality; but, in spite of this conventional opinion, I hold that the healthy sign of an activity of mind in early youth is not to be striving after unheard of miracles, but to imitate closely and carefully what is being said and done in the vicinity.

With these thoughts in mind we may appropriately consider some of the old masters in medicine and the books they wrote. For this purpose no period could serve better than that golden age when Padua was the magnet that attracted students from all parts of Europe.

Let us view Padua as it is today and recall what it was in the sixteenth and seventeenth centuries; let us study the lives of its eminent teachers, who, some three hundred years ago, broke away from the teachings of Galen, which had held sway for fourteen centuries; and let us glance at a few of the books that helped to make medical history.

The University of Padua Today.

After reading the Silliman Lectures on "The Evolution of Modern Medicine", delivered by Sir William Osler at Yale in 1913, I looked forward impatiently to the time when I should be able to visit Padua and see for myself the university where Vesalius, Fabricius, Harvey and others worked in the sixteenth and seventeenth centuries. The opportunity came in 1936, and I shall look back on my visit to Padua as a most memorable occasion.

Fortunately the university was not in session, so that my wife and I were able to wander alone and in leisurely manner through the courts and halls of the old school, with but occasional guidance from an obliging caretaker.

The walls of the main hall, from floor to ceiling, are covered with stemmata or coats of arms of

former students. Some of these stemmata are beautifully made, the blending of gilding and various colours being most attractive.

After hunting in vain for Harvey's stemma in this hall, we continued our search in the corridors and in the arcades surrounding the quadrangle. The walls and ceilings of these arcades are covered with stemmata, some of them unfortunately showing signs of wear. At last our efforts were crowned with success, and there was Harvey's stemma before our eyes. It was rather difficult to find, but would have been less so had we remembered Osler's precise instructions:

> Standing in the arcade on the side of the "quad" opposite the entrance, if one looks on the ceiling immediately above the capital of the second column to the left there is seen the stemma . . . put up by a young Englishman, William Harvey, who had been a student at Padua for four years.

The next thrill was experienced on entering the theatre which Newman says was built for Fabricius in 1593 by the Venetian authorities to celebrate thirty years' service, but which Osler says was built by Fabricius at his own expense. It was in this theatre that William Harvey was taught anatomy. The theatre is in good repair. It is small judged by present-day standards, but is admirably arranged to give a good view of the dissecting table placed on the small floor space in the centre of the theatre, which is circular in outline. Tiers rise steeply from the small central floor space almost to the ceiling.

Standing alone on one of the upper tiers in this empty theatre, gazing down on the central table, one's thoughts flew back to the days when students from all parts of the world met here and listened to Fabricius lecturing on anatomy, while Galileo taught mathematics standing on his pulpit or rostrum in the "adjoining *aula magna*". Galileo's rostrum, in its original state, is still there, to be seen by those who are interested.

The University of Padua in the Past.

Sir George Newman, in his essay "A Century of Medicine at Padua", printed privately in 1922 and dedicated to the medical students of Saint Bartholomew's Hospital, London (on the staff of which William Harvey served as a physician from 1609 to 1643), gives an admirable account of Padua in the past.

In the fourteenth century, he tells us, there were two universities at Padua; that of the humanists (including medicine) was subordinate to that of the jurists, which was larger and richer. The students in each university were enrolled as "nations", each nation electing *concilarii,* who formed with the rectors the executive of the university. In the fifteenth century *collegia* or hostels were established, and Padua became the university town of Venice and one of the great universities of the world.

One of the earliest English students to receive a medical education at Padua (towards the close of the fifteenth century) was Thomas Linacre, who founded the College of Physicians of London in 1518. Linacre was educated at Oxford and lived for some years in Italy. He spent a year in Florence at the court of Lorenzo the Magnificent, where, as Osler says, he may have sat at the same board as Michelangelo. From Florence he went to Rome, where he had access to the Greek manuscripts of Galen's work, which he translated and published at a later date. From Rome he went to Padua, where he received his medical education. On returning to England he shared in the revival of learning and became famous as a great medical humanist and as a distinguished grammarian. According to Osler, he suffered in old age from stone in the bladder, and it is thought that Robert Browning, in his poem "A Grammarian's Funeral", had Linacre in mind when he wrote:

> Back to his book then; deeper drooped his head:
> Calculus racked him:
> Leaden before, his eyes grew dross of lead:
> Tussis attacked him.
> "Now master, take a little rest!"—not he!
>
> . . . . . .
>
> Not a whit troubled,
> Back to his studies, fresher than at first,
> Fierce as a dragon
>
> . . . . . .
>
> So, with the throttling hands of death at strife,
> Ground he at grammar;
> Still, thro' the rattle, parts of speech were rife:
> While he could stammer.

Linacre was followed by John Caius, who, from 1539 to 1541, worked under Vesalius, with whom he lodged. He became renowned as an anatomist and as a classical scholar. Newman tells us that he refounded Gonville and Caius College, Cambridge, was physician to Queen Elizabeth and president of the College of Physicians.

There is a tendency for medical men to lay special stress on the part played by the University of Padua in medical progress; but this university's share in the advancement of learning generally must not be overlooked.

Padua in English Poetry.

Spielman, in his book "The Iconography of Andreas Vesalius", reminds us that more than a century and a half before Vesalius journeyed into Italy, and as long after the university was founded, the name of Padua as a cradle of modern poetry had been enshrined in Chaucer's immortal verse. Spielman adds that when the poet was in Lombardy on his diplomatic mission (somewhere about 1372) Petrarch was at Argua, close to Padua. In the prologue to "The Clerk's Tale" the Sire Clerk of Oxenford says in reply to his host's request:

> I wol yow telle a tale which that I
> Lerned at Padwe of a worthy clerk,
> As preved by his wordes and his werk;
> He is now deed and nayled in his cheste,
> I prey to God so yeve his soule reste!
> 'Fraunceys Petrak, the lauriat poete,
> Highte this clerk whos rethorike sweete
> Enlumyned al Ytaille of poetrie,

Shakespeare, in "The Taming of the Shrew", set the first scene in Padua. Lucentio, addressing his servant, says:

> Tranio, since, for the great desire I had
> To see fair Padua, nursery of arts,
>
> . . . . . .
>
> Here let us breathe, and haply institute
> A course of learning and ingenious studies.
>
> . . . . . .
>
> Tell me thy mind; for I have Pisa left,
> And am to Padua come, as he that leaves
> A shallow plash to plunge him in the deep,
> And with satiety seeks to quench his thirst.

According to Spielman, the library at Padua possesses one of the three copies that exist of the first folio of Shakespeare's plays; the others are at the Bibliothèque Nationale de Paris and the (Royal) Library at Berlin.

The Influence of Padua on the Writing of Great Books.

Many books of this period serve as landmarks in the history of medicine; probably the two most outstanding are *"De Humanis Corporis Fabrica"* of Vesalius, published at Basle in 1543, and the *"De Motu Cordis et Sanguinis in Animalibus"* of William Harvey, published at Frankfurt in 1628.

Vesalius and his "De Fabrica".

Andreas Vesalius was a Belgian, born in 1515, at Brussels. His father was an apothecary, and his mother, according to Newman, was an Englishwoman named Isabella Crabbe. He was educated at Louvain and Leyden, studied medicine in 1533 under Sylvius in Paris, and in 1537 went to Italy, where he received his degree of doctor of medicine at Padua in December of the same year and was elected to the chair of anatomy and surgery at the age of twenty-four.

When he was at Venice in 1537 he attended a hospital which was controlled by the Theatiner Order, to which, at this time, Ignatius Loyola was attached. As Osler stated:

> In the wards of the hospital and the quadrangle, the fiery dark eyed little Basque must frequently have come into contact with the sturdy young Belgian. . . . Both were to achieve phenomenal success—the one in a few years to revolutionize anatomy, the other within twenty years to be the controller of universities, the counsellor of kings, and the founder of the most famous order in the Roman Catholic Church.

Vesalius saw, as no one before him had done, that to know the human body and its working one must first know its parts—its fabric. With this in mind he dissected and studied intensively for some years, and in 1543 published his remarkable book *"De Humanis Corporis Fabrica"*. In Osler's words:

> The worth of a book, as of a man, must be judged by results, and, so judged, the "Fabrica" is one of the great books of the world, and would come into any century of volumes which embraced the richest harvest of the human mind. In medicine it represents the full flower of the Renaissance. As a book it is a sumptuous tome—worthy setting of his jewel—paper, type and illustration to match.

The illustrations, which are a special feature of the *"Fabrica"*, were drawn by Stephan van Calcar, a fellow countryman, who, according to Paul D. White, was a pupil of Titian in Venice.

In 1555 Vesalius brought out the second edition of the *"Fabrica"*, which is described by Osler as even more sumptuous than the first. An excellent copy of the second edition is in the library of Dr. L. Cowlishaw, to whom this country is indebted for his example in collecting old medical books, and for the stimulus he has given to the study of the history of medicine.

Harvey and his "De Motu Cordis".

Though William Harvey was an Englishman, born at Folkestone in 1578, the foundations of his unique work were laid in Padua. Harvey, according to Newman, was a member of the more aristocratic *universitas juristarum*, which admitted a few selected medical students to its ranks, and was chosen a *concilarius* of the English "nation". He worked under Fabricius, who was the first to recognize the valves in the veins as general structures in the venous system. Fabricius called the valves little doors—*"ostiola"*. Harvey had probably seen Fabricius demonstrate these valves, and, as Osler suggests, he may have helped to make the dissections for illustrations of the book *"De Venarum Osteolis"*, published by Fabricius in 1603. Late in life, according to Osler, Harvey told Boyle that it was the position of the valves of the veins that induced him to think of a circulation.

Harvey graduated at Padua in 1602 and later returned to England. He took his degree at Cambridge, began the practice of medicine, and was elected a Fellow of the College of Physicians and physician to Saint Bartholomew's Hospital. He was appointed Lumleian lecturer to the College of Physicians in 1615; but lectures did not begin until 1616, the year of the death of Shakespeare and Cervantes. The lectures were continued yearly without attracting much notice, and it was not until 1628 that Harvey's immortal book *"Exercitatio Anatomica de Motu Cordis et Sanguinis in Animalibus"* was published at Frankfurt.

The book is a small quarto volume of seventy-four pages, and, so far as book-making is concerned, it is of poor quality as regards both printing and paper; but Osler recognizes its outstanding importance when he speaks of it as "a modest little monograph from which we may date the beginning of experimental medicine".

Paul D. White refers to the *"De Motu Cordis"* as the greatest contribution to medical knowledge of all time. There are, he adds, four other significant points in this book: its brevity, its clarity, its literary merit, and its postponement for years until the author believed that he had ascertained all the possible facts and that the time was ripe.

Harvey's humility is well exemplified in the following passage from Chapter I (Leake translation):

Finally, if my work may be helpful to this phase of literature, it may perhaps be granted that I have not lived idly. As the old man in the comedy says:

> For never yet hath any one attained
> To such perfection, but that time, and place,
> And use, have brought addition to his knowledge;
> Or made correction, or admonished him
> That he was ignorant of much which he
> Had thought he knew; or led him to reject
> What he had once esteemed of highest price.
>
> (Willis translation.)

So may it now be regarding the motion of the heart. The path is open for others, starting here, to progress more fortunately and more correctly under a more propitious genius.

The Gold-Headed Cane.

Let us now pass on some two hundred years, from 1628, when the *"De Motu"* was published, to 1827, when the first edition of "The Gold-Headed Cane" appeared. This book is quite different from those already considered in this address; indeed I know of no other medical book that resembles it.

A graduate of the Melbourne medical school to whom I am especially beholden is my colleague, Dr. Geoffrey Davies, pathologist to the Royal Prince Alfred Hospital, Sydney. Not the least of the services he has rendered me was to introduce me to that delightful book by MacMichael, "The Gold-Headed Cane". This book was one of a group of four considered to be peculiarly striking among the many volumes presented by Sir William Osler to the McGill Medical Library. The other three were original editions of works by Vesalius, Linacre and Harvey.

The book is an autobiography of the gold-headed cane which was carried by five eminent medical men over a period of one hundred and thirty years from the time of the abdication of James II to 1823. The first of these was John Radcliffe, of Oxford; the last was Matthew Baillie, nephew of William and John Hunter.

In his introduction to the book George C. Peachy wrote as follows:

> The physician of the late seventeenth century, of whom Radcliffe may be taken as an example, was distinguished by his silk coat, breeches and stockings, buckled shoes, lace ruffles, full-bottomed wig and gold-headed cane, and drove to see his patients in a coach and pair. Before the Restoration he had paid his visits on horseback, sitting side-ways on a footcloth like a woman; but with the opening of the eighteenth century the coach and pair became the chariot and four, or even six, horses.
>
> Symbolic of the wand of Æsculapius, the physician's cane was usually of considerable length, and was provided with a knob, or bar, containing a vinaigrette, which was held to the nose to ward off the noxious vapours arising from the sick-room.

The unique character of the book is made clear in the first chapter, which opens as follows:

> When I was deposited in a corner closet of the Library on the 24th June, 1825, the day before the opening of the New College of Physicians, with the observation that I was no longer to be carried about, but to be kept among the reliques of that learned body, it was impossible to avoid secretly lamenting the obscurity which was henceforth to be my lot. Formerly the entree of palaces had been open to me; I had been freely admitted into the houses of the great and the rich; but now I was doomed to darkness, and condemned to occupy the corner of a library—spacious and splendid, it must be allowed, but where I was surrounded by nothing but the musty manuscripts of defunct doctors.

Later the autobiography continues:

> I shall never forget the first consultation at which I was present; where everything being strange to me, I was attentive to the most minute circumstances. . . . It was in the autumn of 1689. My master, Dr. Radcliffe, had just then returned from a distant journey in the country, and was much fatigued, when an urgent message reached him at his house in Bow-Street, Covent Garden. Snatching me up, he hurried into his carriage, and set off with all speed for Kensington House.

A detailed description of the house and gardens, with notes on their history, is then given, and the narrative proceeds:

> We were ushered through a suite of several rooms, plainly but handsomely furnished, by Simon de Brienne; and it seemed to me that the Doctor assumed a more lofty air, and walked with a firmer step, and I was conscious of a gentle pressure of his hand, as he stopped and gazed for a moment on the likeness of the Founder of the College of Physicians, Dr. Linacre, painted by Holbein, which was hanging in one of the rooms, amongst the royal portraits of the Henrys, and several other of the Kings and Queens of England and Scotland.
>
> On entering the sick chamber, which was a small cabinet in the south-east angle of the building, called the Writing Closet, a person of grave and solemn aspect, apparently about forty years of age, of a thin and weak body, brown hair, and of middle stature, was seen sitting in an arm-chair, and breathing with great difficulty. The naturally serious character of the King (for it was His Majesty William the Third) was rendered more melancholy by the distressing symptoms of asthma, the consequences of the dregs of the small-pox, that had fallen on his lungs.

The King was apparently not above reproach for his manners in his domestic circle. The cane relates that on one occasion, while the Princess, later Queen Anne, was dining one day with the King and Queen, "His Majesty ate up all the green pease, then newly come in, without even once offering that rarity to his royal consort or guest".

These sketches will serve to show the attractive literary style of the author and the intimate insight into the lives of the people of that period which the book provides.

When the new College of Physicians was opened on June 25, 1825, the president, to whose "elegant oration" the cane refers, was Sir Henry Halford, and, although members of the family of George Britton Halford state that there was no relationship between the two, a few references to Sir Henry Halford may be of interest. He is mentioned by Lord Moynihan as one of the minor poets who have been attached to medicine. The statement is attributed to Sir Humphry Rolleston that Sir Henry Halford composed elegant trifles in Latin as he drove from one noble sick-room to another. The photograph of Sir Henry Halford, which I show you, is reproduced from the frontispiece to a book by him entitled "Essays and Orations", read and delivered at the Royal College of Physicians, to which is added an account of the opening of the tomb of Charles I. This small volume was published in 1831.

In 1806 Sir Henry Halford became a member of the club, sometimes distinguished by the title of The Literary Club, which James Boswell, in "The Life of Samuel Johnson", tells us was founded in 1764. Among the original nine members of this club were Sir Joshua Reynolds, Dr. Johnson, Mr. Edmund Burke and Dr. Goldsmith, the last of whom may be taken as an example of those who dabbled with medicine but achieved fame in literature.

Men who Deserted Medicine for Literature.

In Lord Moynihan's Linacre lecture delivered at Cambridge in 1936, entitled "Truants: The Story of Some who Deserted Medicine yet Triumphed", Oliver Goldsmith (1728 to 1774) is included among those who deserted medicine for literature, and with the exception of Keats (1795 to 1821) he is probably the most outstanding member of this group.

Goldsmith was a student at Edinburgh for eighteen months studying chemistry and biology, and an amusing story is told of his first landlady in the northern capital. There is a familiar ring to those who come from Scottish homes in what Smeaton describes in "Famous Edinburgh Students" as Goldsmith's graphic account of the mutations in the culinary art through which in a week a single loin of mutton passed:

> A brandered chop was served up one day, a fried steak another, collops with mutton sauce a third, and so on until the fleshy parts were quite consumed, when finally a dish of broth was manufactured from the bones on the seventh day and the landlady rested from her labours.

From Edinburgh Goldsmith went to the Continent and returned to England with what Moynihan calls "a medical degree of doubtful authenticity"; he tried various occupations without success, then, as Moynihan aptly puts it, "turning to literature for a pittance, he found immortality".

Apparently Goldsmith had much greater facility for writing than for speaking, and, according to Moynihan, Garrick wrote:

> Here lies Nolly Goldsmith for shortness called Noll
> Who wrote like an angel but talked like poor Poll.

Conclusion.

A friend of mine was once invited to deliver an address to celebrate an important event. In his anxiety to do justice to the occasion he lost all sense of time. The result was that, as the address dragged on, a member of the audience turned to his neighbour and said: "Don't you think he is rather long-winded?" To which his neighbour replied: "Long-winded? I think he is encroaching on eternity!" With this in mind I must now close, lest I expose myself to a like rebuke.

In conclusion let me say that one of the underlying themes of this address is homage to old masters, and, young though our country be, there have gone before us in this land men whose example in scholarship, in original investigation, in general culture, is such as to call forth all that is best within us. In this noble company of the past the name of George Britton Halford holds an honoured place.

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THE USE OF SULPHANILAMIDES IN BACTERIAL INFECTIONS.[1]

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In the Bradshaw lecture for 1938, Whitby[68] presented an admirable review of "the most remarkable recent advance in modern therapeutics", namely, the chemotherapy of bacterial infections, and a very full reference was given to the literature available to that time. He had previously[66] [67] presented experimental evidence regarding the efficacy of some of the preparations recommended for use, and Garrod[34] described their clinical application. Reference to these articles is advised; but in view of further advances in chemotherapy and the confusion which still exists in the minds of some practitioners, partly as a result of the influx of advertising literature, an attempt will be made to clarify the present position.

Nomenclature of Amino Compounds.

The original preparation, "Prontosil", now rarely used, was discovered by Domagk and his assistants, and it was soon found that much of its value was attributable to its reduction to p-aminobenzenesulphonamide.[32] This discovery opened the way for further investigation, and the last named compound has become the standard by which other substances are judged.

The preparations now in use may be grouped in three categories: (i) the sulphanilamide group: sulphanilamide, sulphonamide-P, sulphonamide, "Streptocide", and "Prontosil Album" (all are p-aminobenzenesulphonamide); (ii) those in which substitution in the amino group has been made: sulphamido-chrysoidin ("Prontosil"), "Prontosil Soluble", benzyl-aminobenzenesulphonamide ("Proseptasine") and "Soluseptasine"; (iii) those in which the sulphamido group has had one hydrogen atom substituted: "Uleron", 2-(p-aminobenzenesulphamido)pyridine ("M & B 693"), and "M & B 693 Soluble", which is a sodium salt.

Antibacterial Value and Clinical Use of the Various Preparations.

It has been shown as a result of numerous investigations, *in vivo* and *in vitro*, that the first two groups of preparations are inimical to certain strains of hæmolytic streptococci, meningococci, and gonococci, and to type III pneumococci.[66] In addition, there is an increasing volume of clinical

[1] Read at a meeting of the Victorian Branch of the British Medical Association at Yallourn on October 14, 1939.

and experimental evidence pointing to beneficial effects in infections with staphylococci, in typhoid and paratyphoid fever, in brucella infections, in actinomycosis and gas gangrene, and in urinary infections with *Bacillus coli* and *Proteus vulgaris*.[68] There is no evidence that they are of value in virus infections; but secondary infections in these diseases may be influenced by their use.

Sulphanilamide is rapidly absorbed (the ordinary dose taking about four hours), is widely distributed throughout the body fluids and secretions, and is excreted completely in the urine in twenty-four hours, if renal function is normal, in both a free and an acetylated form. The effect of one dose persists for about six hours. Estimation of the quantity in the blood and biological fluids can be determined accurately,[45][68] and this estimation may be an important consideration in controlled therapy because of variations in absorption and elimination and the necessity for an adequate concentration (about 10 milligrammes per 100 cubic centimetres) in the blood in order to obtain a satisfactory clinical result.

As a rule, the dose of sulphanilamide should not exceed five grammes in the twenty-four hours; but it may be calculated on the basis of a total daily dosage of one gramme per twenty pounds of body weight for the first two or three days, with reduction of the dose thereafter. Children require at least a 50% larger dose than adults. It is probable that this dose is rather in excess of requirements. Oral administration is to be preferred, but may need to be supplemented by injections.

"Proseptasine" is much less soluble than sulphanilamide, but is readily absorbed, especially if powdered finely, and is less toxic than sulphanilamide, whilst equally effective against streptococci, both clinically and experimentally.[66] It appears to be effective clinically in meningococcal infections, and good reports have been presented in cases of meningitis and in cervical actinomycosis.[68] "Soluseptasine" is comparable in its clinical effects, and has been reported to be entirely non-toxic even in very large doses. "Prontosil" has no advantage over sulphanilamide, and as "Prontosil Soluble" penetrates the spinal theca more slowly than sulphanilamide, it has no great advantage. While "Prontosil" is transformed in part to sulphanilamide, the action of "Proseptasine" is not due to its reduction to this substance.

Of the preparations in the third group, "Uleron", which is not broken down to sulphanilamide, is much more toxic than the latter, and even when it is given in short courses of four to five days' duration, polyneuritis occurs. It is held to be efficacious in staphylococcal infections; but it is doubtful whether it is more effective than "M & B 693", and it has no advantage over the latter in gonorrhœa. It should not be used as a routine measure.

"M & B 693", 2-(p-aminobenzenesulphonamide) pyridine or 2-sulphanilylpyridine, is highly active against pneumococci of several types and active in equal or even greater degree against bacteria affected by the other groups of drugs.[67] It also appears to be effective in infections with *Streptococcus viridans* and *Hæmophilus influenzæ*. It is relatively non-toxic, but has the disadvantage of being insoluble. Despite the insolubility it is absorbed more rapidly than sulphanilamide. A soluble sodium salt has been prepared which can be given intramuscularly in a 33·3% solution (one gramme in three cubic centimetres) and 0·15 to 1·0 gramme is administered each third or fourth hour.[33] Injection is not painless, but is well tolerated, and an average concentration in the blood of four milligrammes per 100 cubic centimetres has been obtained after the fourth injection. It is recommended that large initial doses of the drug should be given when the oral route is used so that five grammes will be given in the first twelve hours in doses of 2·0 grammes, 2·0 grammes and 1·0 gramme at intervals of four hours. This dosage will usually result in a concentration of 8·0 milligrammes per 100 cubic centimetres in the first twelve hours. Subsequent doses for the adult should, if possible, be 1·0 gramme every four hours; but smaller doses are often necessary and have been effective. With full doses 23 grammes are given in one week. No drug is present in the blood twenty-four hours after treatment is stopped. It is excreted in the urine as free drug and in an acetylated form.

It will be evident that although "M & B 693" appears to be the preparation with the "gun-shot" effect, and is less toxic than sulphanilamide, it is essential that a careful bacteriological examination should be made when the use of these compounds is contemplated. Without bacteriological control rational therapy cannot be undertaken, and as will be seen later, "M & B 693" is not well tolerated by some patients. "M & B 693" is a relatively recent addition to the therapeutic equipment, and serious toxic effects may become more evident as its use increases.

Toxic Effects: Prophylaxis and Treatment.

Sulphanilamide.

Quite a formidable array of toxic manifestations from the use of sulphanilamide has been reported over the past two years. Minor symptoms are common, especially among ambulatory patients, and these take the form of nausea, dizziness, disorientation and mild intoxication comparable to alcoholism. Mild acidosis is common, and this may be obviated by the administration of ten grains of sodium bicarbonate with each four-hourly dose of the drug. These manifestations, and cyanosis, are not indications to cease administration of the drug. Fever is common, usually about the seventh to the tenth day, but may occur as early as the fourth and as late as the thirteenth day; and malaise, skin irritation, and tinnitus are noticed during the fever. This fever may cause difficulties in the treatment of febrile patients, and Hageman and Blake[36] considered it to be a specific reaction.

Cyanosis is due to sulphæmoglobinæmia or methæmoglobinæmia or both, and the former is the

commoner.[7][9][18][54] Archer and Discombe[7] described the methods to be adopted to prevent sulphæmoglobinæmia. Briefly, it is essential to avoid liquid stools which can putrefy with the formation of hydrogen sulphide. A low residue diet (of high caloric value) should be given, and eggs should be limited to one or two per day. Liquid paraffin is the aperient of choice; phenacetin and acetanilide, which may cause sulphæmoglobinæmia, must not be given. Treatment of methæmoglobinæmia is discussed later.

Disorders of the hæmatopoietic system are much more serious; toxic effects and several cases of acute hæmolytic anæmia have been described. Harvey and Janeway[39] described three cases, Long and Bliss[48] four cases, Kohn[41] one case, and Wood[69] reported 21 cases occurring among 522 persons treated with sulphanilamide. The anæmia became manifest from the third to the seventh day, with evidence of hæmolysis, and the earliest signs could be detected within twenty-four to seventy-two hours of the commencement of treatment. Blood transfusion was necessary and was curative; but administration of the drug was stopped in every case. Jennings and Southwell-Sander[40] described three cases of non-hæmolytic anæmia, two of which were hypochromic; the third was a leucoerythroblastic anæmia: all patients recovered.

On the other hand, Campbell[17] has found that moderate doses of sulphanilamide may stimulate a slight rise in reticulocytes which is not necessarily associated with anæmia or leucopenia, and French[30] reported that, in scarlet fever, little deleterious effect on the blood was noticed excepting on the polymorphonuclear leucocytes, the numbers of which were depressed slightly but constantly, especially in the early weeks.

In view of ten reported cases of agranulocytosis,[10][14][30][40][60] mostly fatal, it is of interest to note that French's observations in scarlet fever are in accord with those of Bigler, Clifton and Werner,[11] and Britton and Howkins,[15] who found a transient polymorphonuclear leucopenia. Fleming[28] noted no deleterious effect on the activity of leucocytes *in vitro* with concentrations up to 1 in 4,000. Agranulocytosis occurs after very large and prolonged dosage, or in susceptible patients, and is comparable to the agranulocytosis due to amidopyrine. In order to avoid these serious disturbances it is essential that blood counts and films be taken repeatedly, and frequent estimations of the hæmoglobin should be made especially during the first week of treatment.

Scott and Meerapfel[59] reported a curious alteration in the serum of two patients, in whom the erythrocytes of previously compatible and like group donors were temporarily agglutinated by the patients' serum. They found that normal serum treated *in vitro* with sulphanilamide for four days or more agglutinated erythrocytes of corresponding blood groups and universal donors.

Dermatitis may be a rather distressing and even a serious result from administration of sulphanilamide, and several instances of exfoliative dermatitis comparable to that resulting from arsenical preparations have been described.[27][29][35][48][51] The exfoliative type is consequent upon the commoner types which range from slight cutaneous irritation to purpuric forms. Photosensitization is a result of the use of sulphanilamide,[52] and it is essential for the patient to avoid exposure to direct or artificial sunlight. Erskine[24] reviewed 36 cases occurring during three years at Guy's Hospital, and in addition to photosensitization reported urticarial, morbilliform (with albuminuria), maculo-papular and purpuric, scarlatiniform, rubella-like, papulo-erythematous, and erythematous dermatitis. The skin eruption occurs eight to fourteen days after the commencement of treatment, usually from the eighth to the tenth day, and may be associated with sneezing, photophobia and a rise in temperature of three or four degrees. The frequency of the occurrence of dermatitis is thought to depend to some extent on the efficacy of the compound, and in the exfoliative types a prolonged course of administration and heavy dosage are notable. Administration of the drug should be stopped if a skin rash develops; but later resumption of the same preparation may have no ill effect. Urinary tract irritation and hæmaturia have occurred. Mild sensory manifestations in the form of paræsthesiæ are not serious and do not necessitate cessation of treatment.

It cannot be stressed too urgently that only reliable preparations must be used, and 93 deaths following the use of "Elixir of Sulfanilamide" (Massengill)[56] in the United States of America, should be a sufficient warning.

"Proseptasine", "Soluseptasine", "Prontosil Soluble".

Very mild general symptoms may result from the use of "Proseptasine"; but the possibility of serious effects is very small with it, and "Soluseptasine" is almost innocuous in this respect. Long and Bliss[48] stated that " 'Prontosil Soluble' has but one toxic effect, *viz.*, fever".

"Uleron" and "M & B 693".

Probably sufficient has already been said about "Uleron", for despite careful regulation of dosage and short periods of treatment, peripheral neuritis of some severity has been reported in German literature as well as in English.[63]

"M & B 693" has not as yet been reported as causing serious toxic effects; but headache, cyanosis, nausea, troublesome vomiting and dermatitis occur. Thompson[62] reported rashes resembling measles and rubella, and a rash like that of scarlet fever followed by acute exfoliative dermatitis and photosensitivity. "M & B 693" does not show the same tendency to increased porphyrinuria and light sensitization as does sulphanilamide. Vomiting may be obviated by the following means: the tablets may be crushed and the powder given in milk; a small amount of sodium bicarbonate or gastric sedative may be given with each dose; the powder may be administered in rice-paper capsules; or

effervescent glucose solution may be given as the vehicle or immediately after each dose. Sometimes by the use of more frequent smaller doses nausea and vomiting may be avoided. It is of interest that although local gastric irritation is the probable cause of vomiting in many instances, vomiting has occurred from the parenteral administration of "M & B 693 Soluble"; this indicates a central origin.[33]

Fleming[28] found no evidence of any deleterious effect on the leucocytes *in vitro*, and Evans and Gaisford[25] were unable to detect any difference between the serial white counts in treated patients and control patients with pneumonia. I have not been able to find reports of any harmful effect on the erythrocyte system other than alterations in pigments.

Cyanosis, as already mentioned, is common during treatment with sulphonamide compounds; but whereas with sulphanilamide sulphæmoglobinæmia is chiefly responsible, with "M & B 693" methæmoglobinæmia is practically entirely the cause.[6] The abnormal pigment is readily detected spectroscopically, even in a concentration of 0·4 gramme per 100 cubic centimetres. Bensley and Ross[9] reported that 22% of the hæmoglobin in a patient with pneumonia treated by "M & B 693" was taken up with the abnormal pigment. Hartmann and others[38] stated that the deprivation of oxygen-carrying power with large doses of sulphanilamide may be up to 37% (Wendel[64] stated 40%), and that the majority of patients receiving more than 0·1 gramme per kilogram of body weight in twenty-four hours become cyanosed. Wendel[64] found no correlation between the concentration of sulphanilamide and the intensity of methæmoglobinæmia. Wendel, and Hartmann and his collaborators have studied the effect of methylene blue in methæmoglobinæmia, and Campbell and Morgan[18] have also used this substance with dramatic results. Methylene blue is preventive as well as curative, and although there is a variation in the recommended dosage, its administration is simple and, with certain precautions, safe. For intravenous use, 1·0 to 2·0 milligrammes per kilogram of body weight in a 1% solution is recommended; but Campbell and Morgan gave 350 to 400 milligrammes intravenously or intramuscularly. Methæmoglobin was rapidly reconverted to oxyhæmoglobin, so that in thirty to forty-five minutes the blood pigments had returned to normal. Care must be taken to give the intravenous injection slowly and carefully and to avoid extravenous leakage, which is painful. Too rapid injection causes hives and a severe burning sensation in the lips. Orally, a dose of 1·0 gramme daily, or one to two grains (65 to 130 milligrammes) repeated every four hours, is preventive and curative. No effect is obtained in sulphæmoglobinæmia.

Specific Chemotherapy.

The response of streptococcal infections to adequate treatment is now acknowledged. In septicæmia the drug of choice is "M & B 693"; but in view of the occasional intolerance, sulphanilamide or "Proseptasine" may be preferred. Adequate dosage is essential and administration by day and night is necessary. Oral administration may be supplemented by injections of "Soluseptasine" or "Prontosil Soluble". Control by estimation of the concentration in the blood is advisable, and methylene blue should be given if cyanosis occurs. Septicæmia due to any type of bacterial infection should be treated with one or other of the preparations and very prolonged treatment may be necessary. Erysipelas responds to sulphanilamide; but "Proseptasine" is to be preferred in mild cases and for elderly and enfeebled subjects, especially if renal insufficiency is present.

In scarlet fever complications are a positive indication for treatment; but during the acute stage of the illness antitoxic serum is indicated and sulphanilamide or "M & B 693" may be given with possible advantage.

Respiratory infections are amenable to treatment, but not all patients respond satisfactorily. Acute *otitis media*, acute mastoiditis, acute sinusitis and acute tonsillitis respond to amino compounds, in varying degrees, but bacteriological diagnosis is essential in the first three, and surgical intervention must not be withheld in the presence of positive indications. Proved methods of treatment must still be used; chemotherapy is merely an adjuvant and should not be used indiscriminately. For example, it is often quite superfluous to use the drugs in early *otitis media*, in which simple paracentesis results in rapid cure. Chemotherapy is advisable in fulminating purulent inflammation or when there is any sign of an inadequate response to simple drainage.[30] I have seen acute frontal sinusitis due to infection with *Staphylococcus aureus* respond to conservative drainage and chemotherapy. It has been found that "Proseptasine" is much better tolerated than sulphanilamide or "M & B 693" in upper respiratory infections.

Pneumonia has now been treated with "M & B 693" for a sufficient period for some assessment to be possible, and excellent results have been reported.[1][4][5][25][58][61] Our results at the Royal Melbourne Hospital[31] have not been entirely convincing, but lead us to persevere, for the response is dramatic in many cases. The dose recommended by Whitby frequently results in vomiting; but Anderson and Dowdeswell,[5] and Evans and Gaisford[25] have managed satisfactorily with an initial dose of 2·0 grammes followed by 1·0 gramme every four hours. An average total dose of 25·0 grammes was used by the last-named; Anderson and Dowdeswell used an average of 18·3 grammes, the largest dose being 40·0 grammes. Parenteral therapy will be of great value, and Gaisford, Evans and Whitelaw[33] gave 1·0 gramme orally four hours after initial doses by injection. In the reported series the pyrexial period and the mortality rates were reduced. Injections of "M & B 693 Soluble" were effective in pneumonia complicating hæmatemesis.[20] It is unsafe to use sulphanilamide.

In a discussion on recent advances in the treatment of pneumonia,[55] Whitby pointed out that a concentration in the blood of one to three milligrammes per 100 cubic centimetres gave as good a result as 10 to 18 milligrammes per 100 cubic centimetres. The administration must be continued (as with sulphanilamide) for about five days even though the temperature is normal.

The effect of "M & B 693" on pneumococci *in vitro* has been studied by Fleming,[28] and Maclean, Rogers and Fleming.[44] The drug retards the growth of pneumococci and streptococci; leucocytes are necessary for the destruction of cocci, and the effect of "M & B 693" is enhanced if the blood has been rendered immune. Pneumococci vary enormously in sensitivity, and the variation is associated not with the type but with the individual strain. There is a strong case for the combined use of vaccines and "M & B 693" in all cases of pneumonia in man. Bolton[12][13] recently revived interest in the use of vaccine in pneumonia. Pneumococci can readily acquire a tolerance or fastness to the drug and therefore initial doses must be large and every means must be taken to raise the active immunity. A test for the sensitivity of pneumococci has been described[44] and would be a valuable indication of the likelihood of benefit from chemotherapy.

Meningitis must be diagnosed bacteriologically as well as clinically. Streptococcal infection has responded well;[19][53] but drainage of cerebro-spinal fluid must be instituted as well as chemotherapy, and open surgical drainage of any source of infection must be carried out. Meningococcal meningitis has been treated successfully, and Banks[8] has reported controlled series of cases. The indications appear to be in favour of the combined use of amino compounds and immune serum. There is a considerable lag in the concentration of sulphanilamide in the cerebro-spinal fluid as compared with the blood. High concentrations in the fluid have been reported by Allott.[3] Eldahl[23] recommended intrathecal and intramuscular injections of 0·8% sulphanilamide solution; but apart from the possible exception of an initial dose intrathecally this route of administration has little to recommend it and much to condemn it. Either sulphanilamide or "M & B 693" may be used and early treatment and large initial doses are essential.

Many reports of the successful treatment of pneumococcal meningitis have appeared.[16][21][42][46][53][57] Lawton[42] used "Proseptasine" and "Prontosil Soluble". Other reports concern sulphanilamide and "M & B 693", and McAlpine and Thomas[46] recommended infrequent lumbar puncture after the diagnosis had been established. They considered that a concentration of three to eight milligrammes per 100 cubic centimetres in the cerebro-spinal fluid was necessary and that the optimum daily dose was five to six grammes for the first forty-eight hours. Others used larger doses and Cable[16] used "M & B 693 Soluble". Treatment must be continued after the temperature has returned to normal, for the general improvement lags behind the recovery from pyrexia. Dowds[22] reported a fatal case occurring after treatment of pneumonia with "M & B 693" had been stopped following three days of apyrexia, and Aitchison's patient, in whom meningitis complicated empyema, also died.[2]

Meningitis due to other infections, for example, influenzal, should be treated with amino compounds, and preferably with "M & B 693".

Non-venereal genito-urinary infections with *Bacillus coli communis* and *Proteus vulgaris* respond well to amino compounds,[47][68] and the choice of the particular preparation will depend to some extent on the physician's fancy; but from the point of view of safety and from experiments *in vitro* "M & B 693" appears to be the most suitable. It is interesting to note that an effect is obtained *in vitro* if urine is used, while an aqueous solution of the drug is without effect on the organisms. Acute infections respond best, but chronic infections may be eliminated also. A better effect is obtained with alkaline than with acid urine. Mandelic acid sometimes becomes necessary in streptococcal infections, but amino compounds are to be preferred when prostatic infection is present.

The report of the discussion on chemotherapy in gonorrhœa in *The British Journal of Venereal Diseases*[49] presents an epitome of the position regarding sulphonamide therapy in this disease. The consensus of opinion was that sulphonamide had effected a considerable step forward in the treatment of gonorrhœa and was a firmly established advance. The most striking effects were found in the treatment of recent infection in the male. There was a divergence of opinion regarding the best time to initiate the treatment; but whereas with sulphanilamide and "Uleron" it has been advised that treatment should not be commenced until after a few days have elapsed, delay in using "M & B 693" was unnecessary and inadvisable. Results were often dramatic; but apparent cure with subsequent relapse occurred if treatment was inadequate.

"M & B 693" is to be preferred, and the doses must be widely spread over the twenty-four hours. Frequent small doses are tolerated better than larger infrequent doses. Dr. Westmore Stephens informs me that at the Royal Melbourne Hospital the usual daily dose is six tablets of 0·5 gramme for the first week, followed by four tablets per day for the next two weeks if necessary. Ambulant patients manage these doses quite well, headache being the commonest toxic symptom. Cyanosis has not been troublesome. The patients are warned that they must not take any severe opening medicine, expose themselves unduly to the sun, take the tablets for a period longer than seven days without consulting the surgeon, or neglect to report any symptoms of toxicity. The usual treatment with anterior irrigations should be combined with these measures; posterior irrigations may be given later if necessary. "Collargol" (0·75%) is the best fluid for anterior instillation.

The incidence of complications has been greatly reduced, but chemotherapy is disappointing in the treatment of complications apart from epididymitis. Results have been very satisfactory in females, and salpingitis has responded to treatment.

A new German preparation, "Albucid", has been reported as giving excellent results; but experience with its use is limited. "Uleron" is of use in the later stages of the infection, especially if resistance to "M & B 693" or sulphanilamide appears to have developed.

Tests of cure are essential prior to the cessation of treatment.

As has been indicated, there are many other types of infection in which a good response is obtained *in vitro*, and reports covering a wide range of infections, such as malaria, undulant fever, typhoid fever (seven cases were reported by Harries[37]) and paratyphoid fever, gas gangrene, actinomycosis, *lymphogranuloma inguinale, Bacillus Friedländer* infections and even tuberculosis, have appeared. Fenton and Hodgkiss[26] reported recovery from staphylococcal septicæmia after the administration of "M & B 693", and clinical evidence indicates that this drug is to be preferred in staphylococcal infections. Whitby[68] reported benefit without cure in subacute bacterial endocarditis, and I have seen "M & B 693" cause temporary benefit with decreased pyrexia and increased comfort in the same condition due to infection with *Streptococcus viridans*.

There is no clinical or experimental evidence which warrants chemotherapy with these compounds in virus infections, and I am averse to their administion in cases of the common cold unless there is a complicating localized infection. The apparent benefit in some cases is counterbalanced by the decreased sense of well-being and slight toxic symptoms; certainly sulphanilamide should not be given.

I have not been able to obtain any benefit from amino compounds in acute or chronic ulcerative colitis; but at present "M & B 693" is being taken by a young woman on whom an operation for ileostomy has been performed.

Conclusions.

Despite the brilliant clinical results achieved by chemotherapy with amino compounds, it must always be recognized that the actual bacterial infection is not the sole lesion present. Consideration must be given not only to the use of surgical measures and proved medical and nursing treatment, but it must also be remembered that the process of natural healing must take its usual course. Thus the resolution of pulmonary consolidation in pneumonia must follow the normal course; the effects of toxæmia must be overcome; inflammatory exudates must be absorbed; reparative processes must not be retarded. There is a lag in the bacteriostatic effect after the administration of the drug; immunity lags behind the arrest of progressive infection just as improvement in the patient's general condition follows the decrease in pyrexia. The development of immunity must be assisted by active and passive means. Chemotherapy must be continued until the general condition improves, and certainly for several days after the subsidence of fever. It may be necessary to change the drug because of the development of bacterial resistance to the preparation originally employed. Careful bacteriological control is essential for efficient treatment, and biochemical estimation of the concentration in body fluids is desirable and sometimes imperative.

In conclusion it may be laid down that the amino compounds must not be used indiscriminately. Careful selection of the appropriate preparation is necessary, and it should be used only when there are adequate clinical and bacteriological indications of an infection in which its use is supported by clinical and experimental evidence. There must be a full realization of toxic effects; but adequate dosage must be given and the risks from the drug must be carefully weighed against the risk from the infection. Critical analysis of well-kept records is necessary for the evaluation of cause and effect.

Summary.

1. The amino compounds in common use in medical and surgical practice are briefly discussed.

2. The antibacterial value and clinical uses of the various preparations are outlined.

3. The toxic effects of amino compounds and the methods to be used in the prevention and treatment of these conditions are described. Attention is directed to the beneficial effect of methylene blue in the prevention and treatment of methæmoglobinæmia.

4. The treatment of streptococcal infections, of acute upper respiratory and pulmonary infections, of meningitis, and of genito-urinary infections, including gonorrhœa, is discussed, and the possible value in other infections is indicated. An attempt has been made to point out the particular amino compound most suited for the individual types of disease.

5. The importance of the consideration of bacteriology and pathology has been stressed.

References.

(1) A. L. Agranat, A. O. Dreosti and D. Ordman: "Treatment of Pneumonia with 2-(*p*-aminobenzenesulphonamido)pyridine (M & B 693)", *The Lancet*, Volume I, February 11, 1939, page 309.

(2) J. D. Aitchison: "Pneumococcal Meningitis Complicating Pneumococcal Empyema Treated Unsuccessfully with M & B 693", *The Lancet*, Volume I, June 24, 1939, page 1436.

(3) E. N. Allott: "Sulphanilamide Content of the Cerebro-Spinal Fluid during the Treatment of Meningococcal Meningitis", *The Lancet*, Volume II, July 2, 1938, page 13.

(4) G. Alsted: "Type III Pneumococcal Pneumonia. Effect of M & B 693", *The Lancet*, Volume I, April 15, 1939, page 869.

(5) T. F. Anderson and R. M. Dowdeswell: "Treatment of Pneumonia with M & B 693", *The Lancet*, Volume I, February 4, 1939, page 252.

(6) "Methæmoglobinæmia after Sulphanilamide", *The Lancet*, Volume I, May 6, 1939, page 1053.

(7) H. E. Archer and G. Discombe: "Sulphæmoglobinæmia: Its Cause and Prevention, with Special Reference to Treatment with Sulphanilamide", *The Lancet*, Volume II, August 21, 1937, page 432.

(8) H. S. Banks: "Serum and Sulphanilamide in Acute Meningococcal Meningitis", *The Lancet*, Volume II, July 2, 1938, page 7.

(9) E. H. Bensley and J. B. Ross: "Methæmoglobinæmia due to Sulphanilamide Therapy", *The Canadian Medical Association Journal*, Volume XXXVII, July, 1937, page 62.

(10) S. Berg and M. Holtzman: "Fatal Granulocytopenia following Sulfanilamide Therapy", *The Journal of the American Medical Association*, Volume CX, January 29, 1938, page 370.

(11) J. A. Bigler, W. M. Clifton and M. Werner: "The Leukocyte Response to Sulfanilamide Therapy", *The Journal of the American Medical Association*, Volume CX, January 29, 1938, page 343.

(12) J. H. Bolton: "A Preliminary Report on the Value of Stock Vaccine in the Treatment of Pneumonia", *The Quarterly Journal of Medicine*, New Series, Volume VII, Number 26, April, 1938, page 171.

(13) J. H. Bolton: "A Preliminary Report on the Use and Value of Stock Vaccine in the Treatment of Pneumonia", *Royal Melbourne Hospital Clinical Reports*, Volume IX, Number 2, December, 1938, page 125.

(14) J. G. G. Borst: "Death from Agranulocytosis after Treatment with Prontosil Album", *The Lancet*, Volume I, June 26, 1937, page 1519.

(15) C. J. C. Britton and J. Howkins: "Action of Sulphanilamide on Leucocytes: A Report of Fifty Ambulant Patients", *The Lancet*, Volume II, September 24, 1938, page 718.

(16) J. V. Cable: "Pneumococcal Meningitis: A Review of 39 Fatal Cases and a Report of Recovery after Administration of M & B 693 Soluble", *The Lancet*, Volume II, July 8, 1939, page 73.

(17) C. M. Campbell: "Effect of Sulphanilamide on the Blood Picture", *The Lancet*, Volume I, January 29, 1938, page 247.

(18) D. Campbell and T. N. Morgan: "Cyanosis and Sulphonamide Compounds", *The Lancet*, Volume II, July 15, 1939, page 123.

(19) T. Cawthorne: "Streptococcal Meningitis: Sulphanilamide in its Management", *The Lancet*, Volume I, February 5, 1938, page 304.

(20) R. Coope and E. Leather: "Pneumonia Complicating Hæmatemesis Treated with M & B Soluble", *The Lancet*, Volume II, July 8, 1939, page 72.

(21) A. A. Cunningham: "Pneumococcal Meningitis Treated with Sulphanilamide and M & B 693", *The Lancet*, Volume II, November 12, 1938, page 1114.

(22) J. H. Dowds: "Pneumococcal Meningitis Developing During Treatment with M & B 693", *The Lancet*, Volume I, June 24, 1939, page 1436.

(23) A. Eldahl: "Intrathecal Sulphanilamide in Meningococcal Meningitis", *The Lancet*, Volume I, March 26, 1938, page 712.

(24) D. Erskine: "Dermatitis from Sulphonamide Compounds", *The British Medical Journal*, Volume II, July 15, 1939, page 104.

(25) G. M. Evans and W. F. Gaisford: "Treatment of Pneumonia with 2-(*p*-aminobenzenesulphonamido) Pyridine", *The Lancet*, Volume II, July 2, 1938, page 14.

(26) W. J. Fenton and F. Hodgkiss: "Staphylococcal Septicæmia Treated with M & B 693", *The Lancet*, Volume II, September 17, 1938, page 666.

(27) J. O. Finney: "Severe Dermatitis Medicamentosa following the Administration of Sulfanilamide", *The Journal of the American Medical Association*, Volume CIX, Part 2, December 11, 1937, page 1982.

(28) A. Fleming: "The Antibacterial Action in Vitro of 2-(*p*-aminobenzenesulphonamido) Pyridine on Pneumococci and Streptococci", *The Lancet*, Volume II, July 9, 1938, page 74.

(29) L. J. Frank: "Dermatitis from Sulfanilamide", *The Journal of the American Medical Association*, Volume CIX, September 25, 1937, page 1011.

(30) Jane O. French: "Effect of Sulphanilamide on the Blood in Scarlet Fever", *The Lancet*, Volume II, July 15, 1939, page 127.

(31) L. J. Frew: "Treatment of Pneumonia with M & B 693", *Royal Melbourne Hospital Clinical Reports*, Volume X, Number 1, June, 1939, page 87.

(32) A. T. Fuller: "Is *p*-aminobenzenesulphonamide the Active Agent in Prontosil Therapy?" *The Lancet*, Volume I, January 23, 1937, page 194.

(33) W. F. Gaisford, G. M. Evans and W. Whitelaw: "Parenteral Therapy with M & B 693 Soluble", *The Lancet*, Volume II, July 8, 1939, page 69.

(34) L. P. Garrod: "The Chemotherapy of Bacterial Infections", *The Lancet*, Volume I, May 14, 1938, page 1125; *ibidem*, May 21, 1938, page 1178.

(35) M. H. Goodman and C. S. Levy: "The Development of a Cutaneous Eruption (Toxicodermatosis) during the Administration of Sulfanilamide: Report of Two Cases", *The Journal of the American Medical Association*, Volume CIX, September 25, 1937, page 1009.

(36) P. O. Hageman and F. G. Blake: "A Specific Febrile Reaction with Sulfanilamide", *The Journal of the American Medical Association*, Volume CIX, August 28, 1937, page 642.

(37) E. R. Harries, R. Swyer and N. Thompson: "Sulphanilamide in Typhoid Fever", *The Lancet*, Volume I, June 10, 1939, page 1321.

(38) A. F. Hartman, A. M. Perley and H. L. Barnett: "A Study of Some of the Physiological Effects of Sulfanilamide. II: Methemoglobin Formation and its Control", *The Journal of Clinical Investigation*, Volume XVII, November, 1938, page 699.

(39) A. M. Harvey and C. A. Janeway: "The Development of Acute Hemolytic Anemia during the Administration of Sulfanilamide (para-aminobenzenesulfonamide)", *The Journal of the American Medical Association*, Volume CIX, July 3, 1937, page 12.

(40) G. H. Jennings and G. Southwell-Sander: "Anæmia and Agranulocytosis during Sulphanilamide Therapy", *The Lancet*, Volume II, October 16, 1937, page 898.

(41) S. E. Kohn: "Acute Hemolytic Anemia during Treatment with Sulfanilamide", *The Journal of the American Medical Association*, Volume CIX, September 25, 1937, page 1005.

(42) F. B. Lawton: "Treatment of a Case of Pneumococcal Meningitis with Sulphanilamide", *Royal Melbourne Hospital Clinical Reports*, Volume IX, Number 1, June, 1938, page 98.

(43) P. H. Long and E. A. Bliss: "Observations upon the Experimental and Clinical Use of Sulphanilamide in the Treatment of Certain Infections", *The Canadian Medical Association Journal*, Volume XXXVII, November, 1937, page 457.

(44) I. H. Maclean, K. B. Rogers and A. Fleming: "M & B 693 and Pneumococci", *The Lancet*, Volume I, March 11, 1939, page 562.

(45) E. K. Marshall, K. Emerson and W. C. Cutting: "Para-aminobenzenesulfonamide. Absorption and Excretion: Method of Determination in Urine and Blood", *The Journal of the American Medical Association*, Volume CVIII, March 20, 1937, page 953.

(46) D. McAlpine and G. C. Thomas: "Pneumococcal Meningitis Treated with M & B 693", *The Lancet*, Volume I, April 1, 1939, page 754.

(47) G. Melton and A. Beck: "Therapeutic Action of M & B 693 in Urinary Infections", *The Lancet*, Volume I, April 15, 1939, page 867.

(48) J. G. Menville and J. A. Archinard: "Skin Eruptions in Patients Receiving Sulfanilamide", *The Journal of the American Medical Association*, Volume CIX, September 25, 1937, page 1008.

(49) Medical Society for the Study of Venereal Diseases: Report of discussion on sulphonamide therapy in gonorrhœa. *The British Journal of Venereal Diseases*, Volume XV, Number 2, April, 1939, page 100.

(50) T. G. Millar: Personal communication.

(51) G. B. Myers, E. C. V. Heide and M. Balcerski: "Exfoliative Dermatitis following Sulfanilamide", *The Journal of the American Medical Association*, Volume CIX, Part 2, December 11, 1937, page 1983.

(52) B. A. Newman and H. Sharlit: "Sulfanilamide: A Photosensitizing Agent of the Skin", *The Journal of the American Medical Association*, Volume CIX, September 25, 1937, page 1036.

(53) G. A. Penington and T. G. Millar: "Recovery from Otogenous Meningitis", *Royal Melbourne Hospital Clinical Reports*, Volume IX, Number 1, June, 1938, page 40.

(54) J. P. J. Peton and J. C. Eaton: "Sulphæmoglobinæmia and Methæmoglobinæmia following Administration of *p*-aminobenzenesulphonamide", *The Lancet*, Volume I, May 15, 1937, page 1159.

(55) G. C. K. Reid and S. C. Dyke: "Pneumococcal Meningitis Treated with M & B 693: Recovery", *The Lancet*, Volume II, September 10, 1938, page 619.

(56) Report of the Secretary of Agriculture: "Deaths due to Elixir Sulfanilamide-Massengill", *The Journal of the American Medical Association*, Volume CIX, December 11, 1937, page 1985.

(57) K. Robertson: "Case of Pneumococcal Meningitis Treated with M & B 693", *The Lancet*, Volume II, September 24, 1938, page 728.

(58) Royal Society of Medicine: Report of a discussion by the Section of Medicine on the treatment of pneumonia, *The Lancet*, Volume I, April 8, 1939, page 822.

(59) G. A. Scott and O. Meerapfel: "The Effect of Sulphanilamide on Blood Serum", *The Lancet*, Volume II, July 29, 1939, page 244.

(60) W. F. Schwartz, C. F. Garvin and S. Koletsky: "Fatal Granulocytopenia from Sulfanilamide", *The Journal of the American Medical Association*, Volume CX, January 29, 1938, page 368.

(61) M. Telling and W. A. Oliver: "Case of Massive Pneumonia, Type III, with Massive Collapse. Treated with 2-(p-aminobenzenesulphonamido) Pyridine", *The Lancet*, Volume I, June 18, 1938, page 1391.

(62) A. R. Thompson: "M & B 693 Rashes", *The British Medical Journal*, July 1, 1939, page 13.

(63) C. T. von Valkenberg and G. A. K. von den Borne: "Polyneuritis after Uleron Treatment", *The Lancet*, Volume II, October 15, 1938, page 889.

(64) W. B. Wendel: "The Control of Methemoglobinemia with Methylene Blue", *The Journal of Clinical Investigation*, Volume XVIII, Number 2, March, 1939, page 179.

(65) A. E. A. Werner: "Estimation of Sulphanilamide in Biological Fluids", *The Lancet*, January 7, 1939, page 18.

(66) L. E. H. Whitby: "An Experimental Assessment of the Therapeutic Efficacy of Amino Compounds, with Special Reference to p-Benzylaminobenzenesulphonamide", *The Lancet*, Volume I, June 26, 1937, page 1517.

(67) L. E. H. Whitby: "The Chemotherapy of Pneumococcal and other Infections with 2-(p-aminobenzenesulphonamido) pyridine", *The Lancet*, Volume I, May 28, 1938, page 1210.

(68) L. Whitby: "Chemotherapy of Bacterial Infections", *The Lancet*, Volume II, November 12, 1938, page 1095.

(69) W. B. Wood: "Anemia during Sulfanilamide Therapy", *The Journal of the American Medical Association*, Volume CXI, November 19, 1938, page 1916.

THE CONCENTRATION OF SULPHANILAMIDE IN THE SALIVA FOLLOWING ORAL ADMINISTRATION.

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IN spite of the sensational results following the use of sulphanilamide in most infections caused by hæmolytic streptococci in man, it appears to be useless in the treatment of scarlet fever in the early stage of toxæmia, though effective in such septic complications as *otitis media*. Since the appearance of a scarlatiniform rash is evidence that considerable amounts of erythrogenic toxin have already been absorbed, and it is certain that sulphanilamide has no specific destructive action on streptococcal toxins, its failure to ameliorate the toxic symptoms is not surprising. If, however, the drug administered by the mouth was capable of inhibiting multiplication of hæmolytic streptococci in the throat, it should have a decisive prophylactic effect. No such action could be demonstrated during an investigation in an institutional outbreak of scarlet fever (Keogh, Macdonald, Battle, Simmonds and Williams, 1939).[1] Two new cases of scarlet fever occurred in an isolation ward, two and five days after all the inmates had been given "Proseptasine" (1·5 grammes daily to children, 3·0 grammes daily to adults, in three doses). Possible explanations of this failure were: (*a*) resistance of the epidemic strain of hæmolytic streptococcus (Griffith, Type II) to sulphanilamide, (*b*) inadequate dosage, (*c*) failure of excretion of sulphanilamide in the saliva. There was no reason to favour any one of these hypotheses; but it happened to be convenient to test the last two experimentally. The only references we could find to work on the sulphanilamide content of saliva were those of Marshall,[2] who states that sulphanilamide resembles urea in its equal distribution throughout the body, and of Marshall, Emerson and Cutting.[3] These workers canalized the salivary ducts of dogs, and in two experiments found in one animal a sulphanilamide content of 15·2 milligrammes *per centum* in blood and 9·2 milligrammes *per centum* in saliva, and in a second, 13·3 milligrammes *per centum* in blood and 7·5 milligrammes *per centum* in saliva. The experiments reported in this paper show that the problem of excretion in man is not simple. They suggest that excretion of sulphanilamide occurs only in the saliva at levels of blood sulphanilamide which vary greatly from subject to subject.

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Method of Estimation in Blood and Saliva.

The method of Werner[4] was used for the estimations. This method gives a quantitative recovery of added sulphanilamide in either blood or saliva providing the colorimeter is used for comparison with the standard (Table I). The use of comparison tubes as an alternative method does not give satisfactory results owing to the difficulty of matching the tubes.

TABLE I.
Recovery of Sulphanilamide Added to Blood and Saliva.

Physiological Fluid Examined.	Sulphanilamide Added. (Milligrammes *per centum*.)	Sulphanilamide Recovered. (Milligrammes *per centum*.)
Blood—		
(i)	1·0	1·0
(ii)	5·0	5·0
Saliva—		
(i)	1·0	1·0
(ii)	5·0	5·0

The blood and saliva were examined from four to twenty-four hours after collection, since preliminary experiments showed that the sulphanilamide content does not alter over a period of twenty-four hours (Table II).

Methods of Administration of Sulphanilamide.

In Tablets.

The first experiments were carried out on patients receiving sulphanilamide by mouth in tablet form. The patients were asked to expectorate for a quarter of an hour prior to collection of the corresponding specimen of blood (Table III).

These results show that under these conditions of administration there is no relationship between the concentrations of sulphanilamide in the blood and saliva. In three cases (VI, XIV and XVII) the concentration in the saliva was higher than that in

TABLE II.
Stability of Sulphanilamide in Blood and Saliva.

Number of Specimen.	Sulphanilamide in milligrammes per 100 cubic centimetres of blood.						Sulphanilamide in milligrammes per 100 cubic centimetres of saliva.			
	Fresh.		24 Hours Later.		48 Hours Later.		Fresh.		24 Hours Later.	
	Free.	Total.	Free.	Total.	Free.	Total.	Free.	Total.	Free.	Total.
1	1·5	2·1	1·4	2·0	1·5	2·1	5·0	6·3	5·0	6·3
2	1·3	1·9	1·3	1·9	1·3	2·0	200·0	263·0	200·0	263·0
3	4·6	5·5	4·5	5·5	4·6	5·5	4·2	5·0	4·2	5·0
4	7·7	10·0	7·2	10·0	7·3	10·0	20·0	25·0	20·0	25·0

the blood, in one (XII) the concentrations in blood and saliva were approximately equal and in the remainder the concentration in the saliva was lower than in the blood.

TABLE III.

Sulphanilamide in the Blood and Saliva after Oral Administration of Tablets.

Case Number.	Sulphanilamide. (Milligrammes *per centum*.)			
	Blood.		Saliva.	
	Free.	Total.	Free.	Total.
I	2·1	3·9	1·4	1·7
II	4·6	6·0	0·8	1·4
III	2·5	4·2	2·3	2·5
IV	1·7	2·3	Nil	0·8
V	0·9	1·0	Nil	<0·3
VI	1·0	1·6	1·5	2·3
VII	2·4	5·0	1·0	1·2
VIII	4·2	5·0	1·3	1·7
IX	1·4	3·1	1·1	1·8
X	1·0	1·3	<0·3	<0·3
XI	2·5	3·1	1·0	1·5
XII	3·0	4·2	2·9	4·0
XIII	2·5	3·9	0·8	1·0
XIV	2·5	3·6	4·2	8·0
XV	2·4	4·2	Nil	Nil
XVI	1·3	2·8	Nil	Nil
XVII	0·9	1·7	1·3	2·5
XVIII	4·2	6·0	3·1	4·4
XIX	0·9	1·0	Nil	<0·3

It was thought possible that the drug might be retained in the mouth, for example, in a tooth crevice or under a dental plate. An attempt was made to demonstrate such retention: eleven patients were each given a one gramme tablet of sulphanilamide by mouth and asked to expectorate for fifteen minutes immediately afterwards. The results obtained are shown in Table IV.

TABLE IV.

Sulphanilamide Concentration in Saliva immediately after Ingestion of a One-gramme Tablet of Sulphanilamide by Mouth.

Case Number.	Sulphanilamide (milligrammes *per centum*) in Saliva.	
	Free.	Total.
I	5·0	6·0
II	0·8	0·8
III	0·6	0·6
IV	200·0	200·0
V	4·2	5·0
VI	11·0	12·5
VII	Nil	Nil
VIII	40·0	45·5
IX	20·0	25·0
X	3·1	3·1
XI	1·3	1·7

It will be seen that in more than half of these subjects the concentration of the drug in the saliva was greater than could possibly be accounted for by absorption and excretion. It appears therefore that if sulphanilamide is given orally in tablet form, a variable amount may be retained in the mouth, and may vitiate attempts to estimate salivary excretion of the drug.

In Gelatine Capsules.

An attempt was made to avoid discrepancies due to retention of the drug in the mouth by giving the sulphanilamide in gelatine capsules. This method did not exclude the possibility of leakage from defective capsules, and gave very incomplete absorption (Table V, Case I) or rather slow absorption (Table VI, Case II) judging by the amount of

TABLE V.

Case I. "M & B 693" (7·5 grammes) in Gelatine Capsules by Mouth. Dose equals 64 Milligrammes per Kilogram of Body Weight.

Time after Administration.	Sulphanilamide. (Milligrammes *per centum*.)			
	Blood.		Saliva.	
	Free.	Total.	Free.	Total.
2 hours	0·7	0·9	<0·3	<0·3
4 hours	0·5	0·8	Nil	Nil
6 hours	0·6	0·9	Nil	Nil
10 hours	0·6	0·8	Nil	Nil
14 hours	0·6	0·6	Nil	Nil
18 hours	<0·3	<0·3	Nil	Nil
24 hours	Nil	Nil	Nil	Nil

sulphanilamide present in the blood. The examination of the urine in Case I confirmed the view that absorption was incomplete. Only one specimen of urine in the 24 hours contained sufficient sulphanilamide to be estimated (25 milligrammes in 240 cubic centimetres), the remainder of the 24 hours' output containing traces only. The output of the drug in the first specimen of saliva in Case II, Table VI, may possibly be attributable to its escape from a faulty capsule in the mouth, or to regurgitation from the stomach, since no significant output occurred later when the concentration in the blood was higher.

TABLE VI.

Case II. "M & B 693" (7·5 grammes) in Gelatine Capsules. Dose equals 50 Milligrammes per Kilogram of Body Weight.

Time after Administration.	Sulphanilamide. (Milligrammes *per centum*.)			
	Blood.		Saliva.	
	Free.	Total.	Free.	Total.
2 hours	3·9	3·9	2·8	2·8
6 hours	3·9	4·2	<0·3	0·4
8 hours	4·2	5·5	<0·3	<0·3
12 hours	3·9	4·6	<0·3	<0·3
16 hours	3·9	6·3	<0·3	<0·3
20 hours	4·2	5·2	<0·3	<0·3
24 hours	3·0	4·2	<0·3	<0·3
30 hours	2·1	2·8	<0·3	<0·3

By Rehfuss Tube.

It was therefore decided to use a modification of the procedure of Bazeley,[5] which had been found to give regular and rapid absorption in the horse, so that doses given on a body weight basis gave comparable blood concentration curves (Bazeley, Splatt and Jakobowicz[6]).

The required dose of powdered sulphanilamide was suspended in 100 cubic centimetres of distilled water. A Rehfuss tube was passed and the drug was injected through it by means of a syringe and washed down by a further 100 cubic centimetres of distilled water. The tube was withdrawn and the mouth was well rinsed to remove any sulphanilamide that might have adhered to the end of the tube.

The blood concentration curve in man closely resembles that in horses given approximately the same dose by this method, and the concentration of sulphanilamide in the blood varies with the dose per kilogram of body weight (Figure I). In the horse it was found that a single daily does was just as efficient in maintaining a required blood concentration as was the dose divided in half and given at intervals of eight hours. Doses of six grammes (80 milligrammes and 104 milligrammes per kilogram of body weight) given to two patients maintained for 17 and 8 hours respectively high concentrations of the drug (5·0 to 8·5 milligrammes per 100 cubic centimetres) without the occurrence of any untoward symptoms.

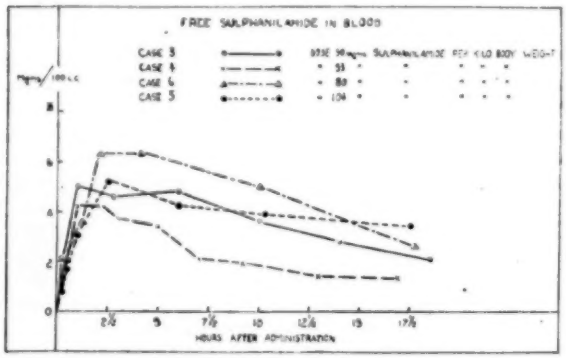


FIGURE I.

Results of Administration by Rehfuss Tube.—The first two patients (Cases III and IV) were each given four grammes of sulphanilamide in a single dose (equivalent to 50 milligrammes and 53 milligrammes per kilogram of body weight). One of these had no estimable concentration of sulphanilamide in the saliva at any time (Case III, Table VII) and the other, in which a higher level was reached in the blood, showed a measurable amount

TABLE VII.
Case III. Sulphanilamide (4 grammes) by Rehfuss Tube. Dose equals 50 Milligrammes per Kilogram of Body Weight.

Time after Administration.	Sulphanilamide. (Milligrammes *per centum*.)			
	Blood.		Saliva.	
	Free.	Total.	Free.	Total.
1 hour	4·2	5·9	<0·3	<0·3
2 hours	4·2	5·0	<0·3	<0·3
3 hours	3·7	4·1	<0·3	<0·3
5 hours	3·4	3·9	<0·3	<0·3
7 hours	2·1	2·8	<0·3	<0·3
9 hours	1·0	2·5	<0·3	<0·3
13 hours	1·4	1·9	Nil	Nil
17 hours	1·3	1·5	Nil	Nil
21 hours	0·8	1·2	Nil	Nil
25 hours	0·6	1·1	Nil	Nil

for a short period in the saliva (Case IV, Figure II). By these patients, 2·2 and 2·0 grammes of sulphanilamide respectively were excreted in the urine during 24 hours.

It was thought possible that sulphanilamide might have an inhibiting or stimulating effect on

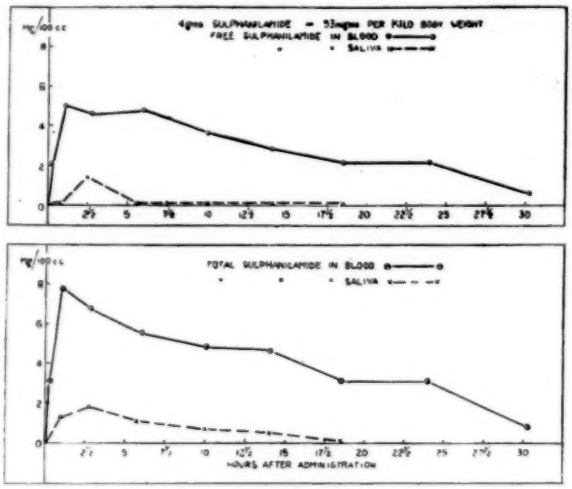
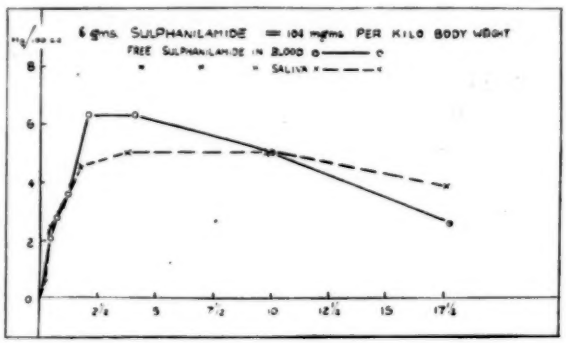


FIGURE II.

the salivary excretion; but estimations of the urea content of the blood and saliva in four cases (Cases



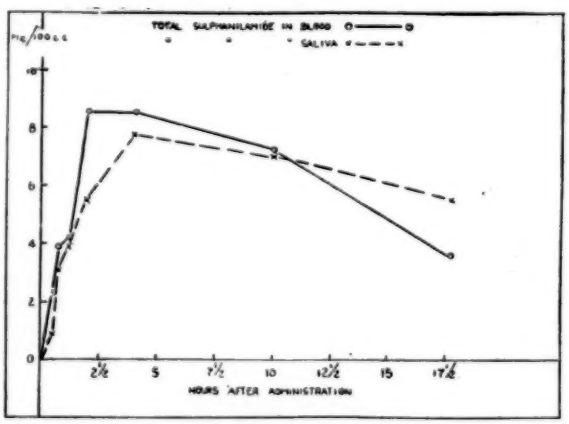


FIGURE III.

IV, VI, VII and VIII) revealed no such disturbance and the volume of saliva excreted was within normal limits. The urea contents of the blood and saliva

were roughly parallel and were within the limits of daily variation observed in normal subjects on normal diets by Drevermann.[7] The results obtained in our first two cases, in which the drug was given by the Rehfuss tube method, suggested the possibility that the excretion of sulphanilamide in the saliva might occur only when the concentration in the blood exceeded a threshold value greater than 5·9 milligrammes per 100 cubic centimetres. The patient (Case III) with a maximum total blood sulphanilamide content of 5·9 milligrammes *per centum* excreted less than 0·3 milligramme *per centum* in the saliva, and the patient (Case IV) with a maximum "total" value of 7·7 milligrammes *per centum* (Figure II) in the blood excreted in one sample 1·8 milligrammes *per centum* in the saliva. The results in the remaining cases indicated that the behaviour of Case III was anomalous and suggested that excretion generally took place at much lower levels, or that the drug tended to be equally distributed in the blood and tissues (Figure III). Two patients (Cases V and VI) were given six grammes of the drug in a single dose. The results are illustrated in Figure III (Case V) and Table VIII (Case VI). In Case V the drug appeared to be uniformly distributed because all the corresponding samples of blood and saliva contained sulphanilamide, which appeared in the saliva when the concentration in the blood was 2·3 milligrammes *per centum* total sulphanilamide, and in Case VI no appreciable amount of the drug was found in the saliva when the level in the blood was 1·9 milligrammes *per centum*, though when the concentration in the blood rose during the next half-hour to 5·0 milligrammes *per centum* the drug was found in the corresponding sample of saliva in significant amounts.

Discussion.

Seven patients were given sulphanilamide by the Rehfuss tube in doses ranging from 40 to 104 milligrammes per kilogram of body weight. The figures obtained for the blood sulphanilamide level were remarkably constant for the same dose and varied with variation in dosage (Figure I); but no such correlation could be observed in respect of salivary excretion of the drug. Table IX shows that at the time the drug reached its maximum concentration in the blood, the concentration in the saliva varied from 6% to 86% of that in the blood in the case of free sulphanilamide, and from 5% to 93% in the case of total sulphanilamide. Conversely (Table X), when the concentration in the saliva was maximal, the free sulphanilamide in the saliva was from 7% to 119% of that in the blood at the corresponding time. If these results are considered from the point of view of a possible threshold in the blood for excretion of sulphanilamide in saliva, the "total" threshold values indicated in the seven patients were greater than 5·9, between 3·1 and 4·6, less than 2·3, between 2 and 5, less than 2·8, less than 3·4, less than 3·5 and less than 2·5 milligrammes *per centum*. In four cases (Cases V, VII, VIII, IX) all the samples of saliva contained the drug, and the results might be interpreted as indicating that in

TABLE VIII.

Case VI. Sulphanilamide (6 grammes) by Rehfuss Tube. Dose equals 80 Milligrammes per Kilogram of Body Weight.

Time after Administration.	Blood.			Saliva.		
	Sulphanilamide. Milligrammes *per centum*.		Urea. Milligrammes *per centum*.	Sulphanilamide. Milligrammes *per centum*.		Urea. Milligrammes *per centum*.
	Free.	Total.		Free.	Total.	
½ hour	0·8	1·7	25	—	—	—
¾ hour	1·7	1·9	27	<0·3	<0·3	27
1 hour ..	3·1	5·0	24	0·9	1·3	23
2½ hours ..	5·2	8·5	26	4·2	5·5	24
5½ hours ..	4·2	6·3	—	5·0	7·2	—
10 hours	3·9	5·5	28	5·0	6·3	27
17½ hours ..	3·4	5·0	25	2·8	3·6	24

TABLE IX.

Comparison of Dosage and Degree of Maximum Concentration of Sulphanilamide in Blood and Saliva at the same Time

Case.	Dose in Milligrammes per Kilogram Body Weight.	Maximum Salivary Sulphanilamide Content. (Milligrammes *per centum*.)		Blood Sulphanilamide Content at Time of Maximum Salivary Sulphanilamide Content. (Milligrammes *per centum*.)		$\frac{\text{Free salivary sulphanilamide}}{\text{Free blood sulphanilamide}} \times 100$	$\frac{\text{Total salivary sulphanilamide}}{\text{Total blood sulphanilamide}} \times 100$
		Free.	Total.	Free.	Total.		
IX ..	40	2·6	3·3	1·5	2·1	58%	64%
VII ..	50	3·3	3·7	1·3	1·4	36%	38%
III ..	50	4·2	5·9	<0·3	<0·3	7%	5%
IV ..	53	5·0	7·7	<0·3	1·3	6%	17%
VIII ..	70	3·6	4·2	3·1	3·9	86%	93%
VI ..	80	5·2	8·5	4·2	5·5	81%	65%
V ..	104	7·3	8·5	4·5	5·5	62%	65%

TABLE X.

Comparison of Dosage and Degree of Maximum Concentration of Sulphanilamide in Saliva and Blood at the same Time.

Case.	Dose in Milligrammes per Kilogram Body Weight.	Maximum Sulphanilamide in Saliva. (Milligrammes *per centum*.)		Sulphanilamide in Blood at Time of Maximum Sulphanilamide in Saliva. (Milligrammes *per centum*.)		$\frac{\text{Free salivary sulphanilamide}}{\text{Free blood sulphanilamide}} \times 100$	$\frac{\text{Total salivary sulphanilamide}}{\text{Total blood sulphanilamide}} \times 100$
		Free.	Total.	Free.	Total.		
IX ..	40	1·5	2·1	2·6	3·3	57%	64%
VII ..	50	1·3	1·4	3·3	3·7	40%	38%
III ..	50	<0·3	<0·3	4·2	5·9	7%	5%
IV ..	53	1·4	1·8	4·6	6·7	30%	27%
VIII ..	70	3·1	3·9	3·6	4·2	86%	93%
VI ..	80	5·0	7·2	4·2	6·3	119%	114%
V ..	104	5·0	7·7	7·3	8·5	68%	90%

these subjects it tended to be uniformly distributed and that there was no real threshold above which the drug was excreted; or alternatively, that if a threshold existed, this was lower than the lowest concentration of sulphanilamide observed in the blood.

The number of patients examined is too small to be adequate as a basis for general discussion of the mechanism of excretion of sulphanilamide in the saliva. The series is, however, sufficiently large to settle one of the points at issue in this investigation—namely, the apparent failure to provide prophylaxis against scarlet fever with this drug. Thus though a dose of six grammes (70 or more milligrammes per kilogram of body weight) appears to ensure excretion of a reasonable amount of sulphanilamide into the saliva, a dose of four grammes (50 milligrammes per kilogram of body weight) was not adequate to cause such a secretion. It is unlikely therefore that the saliva of the adults in the scarlet fever ward who were taking 3·0 grammes of "Proseptasine" daily, or that of the children receiving a dose of 1·5 grammes, contained sulphanilamide in concentrations sufficient to be effective.

Summary.

1. In seven cases the concentration of sulphanilamide in the blood bore a constant relationship to the amount of the drug given.

2. The concentration of sulphanilamide in the saliva bore no constant relationship to the concentration of the drug in the blood.

3. Sulphanilamide causes neither stimulation nor inhibition of the salivary glands as judged by the volume of saliva excreted and the concentration of urea in it.

4. Single doses of sulphanilamide up to four grammes (approximately 50 milligrammes per kilogram of body weight in an average man) sometimes failed to cause any significant excretion of the drug into the saliva, whereas single doses of six grammes (70 or more milligrammes per kilogram of body weight) given with large quantities of water by a Rehfuss tube caused prolonged excretion in the saliva.

Acknowledgements.

Our sincere thanks are due to Dr. C. H. Kellaway, Director of the Walter and Eliza Hall Institute, and to Dr. E. V. Keogh, of the Commonwealth Serum Laboratories, for their generous assistance, and to Dr. C. Wallace Ross for making Dr. Jakobowicz's services available. We should also like to thank the honorary medical staff of Prince Henry's Hospital, Melbourne, who kindly placed some of their patients at our disposal.

References.

(1) E. V. Keogh, I. C. MacDonald, J. Battle, R. Simmons and S. Williams: "Some Factors Influencing the Spread of Scarlet Fever in an Institution", in the press.
(2) E. K. Marshall: "Bacteriological Chemotherapy: The Pharmacology of Sulphanilamide", *Physiological Reviews*, Volume XIX, Number 2, April, 1939, page 240.
(3) E. K. Marshall, K. Emerson and W. C. Cutting: "Distribution of Sulfanilamide in the Organism", *The Journal of Pharmacology and Experimental Therapeutics*, Volume LXI, October, 1937, page 196.
(4) A. E. A. Werner: "Estimation of Sulphanilamide in Histological Fluids", *The Lancet*, Volume I, January 7, 1939, page 18.
(5) P. L. Bazeley: "The Nasopharyngeal Method of Administering Drugs, with Special Reference to Sulphanilamide", *The Australian Veterinary Journal*, October, 1939, page 199.
(6) P. L. Bazeley, B. Splatt and R. Jakobowicz: "Dose Rates and Blood Concentrations of Sulphanilamide in Equines", THE MEDICAL JOURNAL OF AUSTRALIA, November 18, 1939, page 747.
(7) E. B. Drevermann: "Experimental Variation of the Blood Urea", in the press.

Reports of Cases.

RASH FOLLOWING THE USE OF SULPHANILAMIDE.

By J. E. BARKER.

Metropolitan Infectious Diseases Hospital, Northfield, South Australia.

Clinical Record.

THE patient, a female, aged six years, was admitted to the Metropolitan Infectious Diseases Hospital, Northfield, on September 13, 1939, suffering from a moderately severe attack of scarlet fever.

On her admission to hospital the cervical glands were palpable, but small and not tender. The temperature was 102° F., but it fell to within normal limits by the third day and remained there until the twelfth day, from which day its course is shown in the diagram (Figure I).

On the afternoon of the fourteenth day after admission to hospital the patient complained of painful swelling of the neck. The cervical glands were found to be consider-

ably enlarged and tender on both sides. Their subsequent progress is shown approximately in the diagram (Figure I), which also shows the sulphanilamide given in treatment.

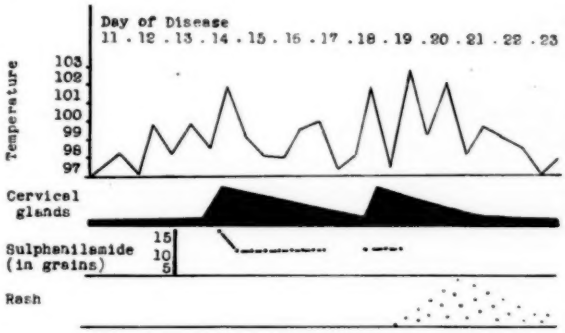


FIGURE I.

On September 30, eighteen days after admission to hospital, the child was inadvertently exposed to direct sunlight for about two hours. On October 1, six days after

FIGURE II.

the commencement of sulphanilamide therapy, small brownish-pink macules were found on the abdomen. Rubella was suspected, in spite of the unusual situation for the

FIGURE III

first appearance of the rash. The lesions closely resembled those of rubella, and exposure to that infection had occurred about sixteen days previously. By the second day the rash was all over the trunk and was spreading to the limbs and face. It had changed in character. The spots were larger brownish papules, with bright red sharply defined edges. In some areas the spots were beginning to run together, giving a polymorphic appearance. A drug rash was now suspected, and this diagnosis was confirmed by Dr. F. H. Beare. On the third day the spots had coalesced further, as shown in the photographs (Figures II and III). The rash was fading from the trunk, but was still bright on the face and limbs. By the fourth day it had almost faded. When cold, the limbs had a blotchy appearance, and this was still noticeable when the child was discharged from hospital about ten days later.

Acknowledgements.

I wish to thank Dr. F. H. Beare and Dr. A. H. Finger for permission to publish details of this case.

DISK-SHAPED MENISCI.

By J. KENNETH MOWAT,
Hay, New South Wales.

Clinical Record.

K.L., an athletic youth, aged seventeen years, injured his left knee by a classical "twist in flexion" at football in August, 1938. Moderate synovitis ensued, causing a complaint of weakness, but there was no pain or locking. A week later the joint locked; the locking caused intense pain lateral to the patellar ligament, and this was followed by sudden unlocking. The patient said that he had had periodic "trouble" in both knees for many years—slight pain and weakness, attributable to minor injuries at various sports. A diagnosis of torn lateral meniscus was made, and the patient travelled to Melbourne, where the meniscus was removed. The surgeon subsequently reported to me that the cartilage was severely torn and removal had been difficult. The lad made a slow but satisfactory recovery and resumed his football.

On July 6, 1939, the right knee was injured in a precisely similar manner to the left. On examination on the following day fluid was found in the joint (regarded as a moderate hæmarthrosis); tenderness was present behind the biceps tendon, and resistance to flexion was met with beyond 90°. The complaint was of pain behind the knee and of weakness, with no locking.

On reviewing the history of trivial injuries and the tear in the left lateral cartilage I made a diagnosis of congenital disk-shaped lateral menisci. Operation was performed three days later.

At operation the joint was found to contain blood and synovial fluid. The semilunar cartilage was of great size and thickness; it covered practically the entire articular surface of the tibia and was torn posteriorly.

The patient suffered much more prolonged pain after this operation than any other similar patient in my experience. In spite of his complete apyrexia I should have been greatly worried but for assurances that his sufferings were as great after the previous operation in Melbourne the year before.

Discussion.

Disk-shaped lateral meniscus is a congenital abnormality which is apparently uncommon. It varies somewhat in shape, but the classical type is the disk observed in this case, with no anterior or posterior horn, a greatly thickened outer border, and the medial border not crescentic.

Opinion seems to differ as to whether the condition is always or only sometimes bilateral. The disk differs from the normal cartilage in the following respects: (*a*) it is prone to tear; (*b*) once torn it is unlikely to

do other than give persistent trouble; (c) it produces intermittent mild attacks of pain, swelling and weakness throughout childhood, and sometimes frequent painless locking.

Reviews.

MINOR GYNÆCOLOGICAL PROCEDURES.

"OFFICE GYNECOLOGY" is described by the author, Dr. J. P. Greenhill, in his preface, as embodying medical gynæcology and the technique of minor operations that can be performed in the physician's office.[1] Printed on the usual heavy quality paper we associate with American productions, the book is pleasant to handle and to read.

Included in the operative section are procedures such as the passage of a sound, the removal of a Bartholinian cyst, and curettage under local anæsthesia, which are not usually considered suitable for other than hospital practice by Australian standards.

There is a chapter on *post partum* care, containing useful comments and details of exercises, which forms a valuable reminder of preventive gynæcology. *Trichomonas vaginalis* infection receives adequate attention. The vinegar douche recommended suggests an old home remedy, but is no doubt as effective as the more usual lactic acid preparations.

The author rightly condemns as futile the treatment of chronic cervicitis by douches and painting, and describes fully and well the various methods of cauterization and electro-coagulation, though the complete coning of the cervix with diathermy knife seems a procedure more suitable for the operating theatre than the consulting room. In another section the subcutaneous injection of alcohol for pruritus is recommended for hospital practice.

There is a very full and well-illustrated chapter on endocrinology and the application of the various hormones to treatment; and there is also a full description of the technique of the hormone tests for pregnancy.

The early diagnosis of cancer of the cervix by the use of the colposcope receives the full and detailed notice it deserves.

Nine pages are devoted to artificial insemination; but the author does not quote results.

A chapter on premarital advice is a new and desirable addition to books of this type.

There is rather a lack of balance in the selection of the subject matter, and the author has obviously written at length on those parts of the subject which hold most interest for himself. It is a book for the specialist, who may find in it some useful hints. For reference by the occasional gynæcologist the subject matter is scarcely comprehensive enough.

MEASUREMENT OF THE REACTION OF THE BODY IN DISEASE.

THE title of the book "The Biological Reaction", by Dr. O. H. Bucher-Trümpler, director of a Swiss tuberculosis institute, and Dr. C. C. Hofflin-Karwatzki, of Canada, gives no clue to the nature of its contents.[2] A first glance might suggest that it was a treatise on acoustics, except that the treatment is geometric and never algebraic; it is quite possible that some skimming readers might dismiss the volume as the work of cranks, but cranks do not collaborate as a rule.

The claims put forward by the authors are sweeping for their geometrical method applied to tuberculosis—diagnosis with detail of foci, active, stabilized, passive or healed; prognosis, classified under several categories; and finally treatment. Immense importance is ascribed to the leucocyte, to which they give the position in pathology which the quantum holds in modern physics.

In 1929 one of the authors, Dr. Hofflin-Karwatzki, in collaboration with George E. Stanley, working in the Disease Research Institute, Hull, Quebec, Canada, announced a direct correlation between monocytes, non-segmented neutrophile cells and tuberculous foci in cattle. We have been unable to find the name of this institute in the list of official and accredited veterinary schools and institutes of Canada, but this may have some simple explanation. The two authors of this book have elaborated this idea into a complex system of geometric analysis, using the counts of the several leucocytes as guides to various body reactions. One principle emphasized in this book cannot be controverted, though it finds small place in physiological and pathological literature, and that is that there are in the body many periodic variables which can be given graphic presentation and to which mathematical methods can be applied. The body in health, but more particularly in disease, exhibits many periodic variables. Why should not these be treated in the manner the physicist regards as necessary, for he asserts as axiomatic that in the discussion of all complex periodic functions the true method of attack is always the device of the Fourier analysis? As Leonar Michaelis remarked in 1922: "one day the Fourier analysis will be used to clear up biological problems because in this field periodic functions are so numerous. The Fourier method makes it possible to transform at least approximately the most complex periodic functions into the most simple, those of the sine and cosine."

The two authors of this book take seven periodic variable factors in tuberculous patients—general resistance, specific resistance, intensity of tuberculous foci, extensity (or, shall we say, number) of foci, allergy, immunity index and finally metabolic index. These are plotted with logarithmic coordinates and integrated so that a single graph results. The authors claim that the nature of this graph, which is highly individual, allows far-reaching conclusions to be drawn. With the theory of this we cannot find fault; rather would we welcome the method as strikingly original; but a doubt will arise whether these same periodic variable factors can be so accurately determined, even when leucocyte counts are used as data, that numerical assessment capable of mathematical handling is attainable. In all fairness it should be stated that the authors are prepared for this criticism and give the probable error for each, this being as high as $\pm$ 42% for specific resistance.

The publishers announce that the medical practitioner will frequently consult this volume. We doubt if in any community 1% of medical graduates have the mathematical equipment to criticize, appreciate or use this laborious geometric technique.

A BOOK ON DIAGNOSIS.

"SURGICAL DIAGNOSIS", by Stephen Power, is an original contribution to our medical literature.[1] The idea of the book, as the author explains, originated from an article written for *The Clinical Journal* on the diagnosis of prostatic enlargement.

The text deals with the diagnosis of conditions arising in various parts of the body, such as the neck, breast, joints *et cetera*. It is by no means complete; but it is full of interesting and intelligent observations based upon clinical experiences.

Whilst this little book is not a necessity, it nevertheless fills a breach in our medical literature, and as such will prove most useful to both student and practitioner.

[1] "Office Gynecology", by J. P. Greenhill, B.S., M.D., F.A.C.S.; 1939. Chicago: The Year Book Publishers. Demy 8vo, pp. 406, with illustrations.

[2] "Die biologische Reaktion. Eine funktionelle Analyse und Synthese biometrischer Werte zur Zahlenmässigen Erfassung von Allergie, allgemeiner Resistenz, spezifischer Resistenz. Krankheitsintensität, Extensität aktiver Herde, Immunität", by O. H. Bucher-Trümpler and C. C. Hofflin-Karwatzki; 1939. Bern: Hans Huber. Imperial 8vo, pp. 262, with illustrations. Price: Schw. Fr. 42.80.

[1] "Surgical Diagnosis", by S. Power, M.S., F.R.C.S.; 1939. Bristol: John Wright and Sons Limited. Demy 8vo, pp. 228, with 51 illustrations and 15 plates.

The Medical Journal of Australia

SATURDAY, JANUARY 27, 1940.

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MORE ABOUT VITAMIN *B*.

THE unfortunate divergences in nomenclature and definition, due to the conduction of investigations by various workers in different countries and with different laboratory animals, are beginning to show some signs of abatement. The twofold approach to analysis, namely, the animal test and the purely chemical, has clarified many issues, as reasonable convergence between the two may be taken to indicate a fair degree of accuracy. The results of recent research are continually being put before the profession, not merely by the appropriate technical journals, but by commercial publications, many of which give a restrained scientific presentation of the facts. One effect of the present war will be to diminish the spate of barbiturates, hormones, vitamins and antiseptics which German firms thrust upon the medical profession throughout the world. Possibly some doctors will miss the trade journals, gratuitously presented with their advertisements intermingled with honest information, though the clinical evidence adduced rarely commanded respect. It is interesting to note that commercial houses in the British Empire can supply the deficiency as far as scholarly résumés of the subject are concerned. Without making invidious comparisons or giving unsolicited advertisements we may mention the excellence of "Vitamins in Medical Practice", issued by Roche Products Limited, and the discussion on vitamin *B* in the Australian booklet entitled "Vegemite". What, then, are some of the leading ideas of today on the vitamin *B* question?

Vitamin B_1, also called aneurin or thiamin, remains the original water-soluble anti-beriberi factor, present in such large amount in rice polishings. Its chemical constitution, occurrence, functions and therapeutic use, and the results of deficiency, have all been worked out in detail. Shortage of this vitamin is perhaps the commonest deficiency in modern diets.

Vitamin B_2 is also called riboflavin, lactoflavin or vitamin *G*. The present tendency is for the name riboflavin to be given preference. The chief source is yeast. The chemical constitution has been established. Unfortunately the function of this vitamin has not been clearly defined, though its close association with Warburg's cytoplasmic enzyme gives a clue to its role. It is a pity that ignorance should be cloaked by the use of the term "growth vitamin"; for all vitamins are growth vitamins, as has been insisted on by Sir Charles Martin. Further research is indicated.

Nicotinic acid is also called pellagra-preventive, or "P.P." The confusion about pellagra has not all been cleared up; but some progress has been made. That human pellagra can be cured by nicotinic acid has been shown by a number of independent observers. A disease of pigs very like pellagra also yields to nicotinic acid, and black tongue in dogs is similarly responsive. The dermatitis of rats, which at one time was supposed to be pellagra, does not improve under nicotinic acid, but shows dramatic abatement on the administration of a yeast factor to which György has given the name vitamin B_6, or "rat antidermatitis factor". In other laboratory animals the presence of this substance, though not associated with the prevention or cure of pellagra, has some say in the general well-being

and is unfortunately listed under the vague term of growth-promoter.

A new factor, L_t, has recently been discovered in the fuller's earth filtrate from aqueous extracts of fish liver. Deficiency in this vitamin causes not only the usual inhibition of growth, but a change of coats in rats, black and whites becoming brown and blacks becoming grey. An announcement at a recent meeting of the Biochemical Society indicates that the vitamin *B* complex still has secrets to be disclosed. When a yeast or liver extract is shaken with norite charcoal the riboflavin is quantitatively removed whilst some hitherto undiscovered *B* factors pass into the filtrate, as indicated by the rat-growth test. The problem is further complicated by the fact that norite charcoal removes from liver extracts not only the riboflavin but a growth factor apparently not present in yeast.

From the standpoint of general nutrition considerable interest attaches to extended investigations made on the vitamin *B* group in fish foods. As is well known, this complex is, like ascorbic acid, present in small amounts in the flesh of mammals, but is abundant in glandular tissues. A curious exception is the pig, whose flesh contains the *B* factors in amounts far exceeding that of other food mammals. Why this should be is not known.

A similar state of things exists in fish foods. The flesh or skeletal muscle is poorly equipped with the *B* vitamins, whereas the liver is rich in them. But one fact of notable interest stands out in these investigations, and that is the high concentration of *B* vitamins in the roe, both male and female. The analogy of seeds in plant life should have led us to expect this; but the results are none the less surprising. The female fish that has discharged its ova, or the male its soft roe, has always been regarded, like the post-parturient female mammal, as unfit for human food, though hitherto there has been no scientific explanation for this, probably sound, tradition. Not many years ago the herring fleets in north-west Europe ceased operations when the herring were "spent" or "shotten"; but today they remain active, as the exhausted herrings are used for kippering. Canned fresh herring has usually a large roe; the kipper rarely. The tradition about the spent herring is recalled by Falstaff's outburst: "If manhood, good manhood, be not forgot upon the face of the earth then am I a shotten herring." That the same concentration of vitamins should be found in the roe of Australian fish is to be expected. This might well be the subject of a useful research.

Current Comment.

THYREOGLOSSAL FISTULA.

IT does not seem strange that the treatment of thyreoglossal fistula has been attended with indifferent success in the past when one considers the inexactitude of our knowledge of the anatomy of the condition and the somewhat unimaginative methods of attack that have been in common use. Yet this abnormality, which is such a trial to its possessor, is not rare, a study of the records of the three teaching hospitals of Sydney having brought to light the histories of 98 patients operated upon for thyreoglossal cysts and fistulæ, of whom 37 had had previous operations. V. J. Kinsella, who made this study, recalls that until comparatively recently it was the accepted practice to treat thyreoglossal fistulæ by attempting to destroy the lining membrane by cautery or caustics.[1] More recently attempts have been made to remove the tract by dissection; but it is very fragile and hard to define, and recurrence is frequent, so that most surgeons now go further and remove part of the hyoid bone and a cylinder of tongue substance in the region the tract is thought to occupy.

Kinsella has made the suggestion that if it could be shown that a thyreoglossal fistula was complete, that is to say, possessed of an opening on the tongue as well as in the front of the neck, it might be well treated by firm closure of the cervical end, the pharyngeal opening being trusted to carry away the secretion; and, despite authoritative statements in the recent literature that no complete fistula with both outer and inner openings has been reported, he has put this suggestion into practice on two occasions. Iodized oil was injected into the fistulous opening in the neck of each of his two patients, and in each case it issued from the dorsum of the tongue. The course of the thyreoglossal tract was demonstrated by X rays. A thin oil, such as "Neo-hydriol", is recommended for this purpose. Kinsella suggests that if a radiographic examination were always made a large proportion of thyreoglossal fistulæ might be found to have a pharyngeal opening. If such an opening be present it is a simple matter to define the tract for a short distance in the front of the neck, apply a ligature, and remove the lower portion, touching the stump with carbolic acid and alcohol. Of Kinsella's two patients, one, whose fistula was simple and previously untouched, is apparently cured, three years after the operation; while the

[1] *The British Journal of Surgery*, July, 1939.

other, whose fistula was arborescent and constricted by involvement in the scar of a previous operation, suffered recurrence.

It is likely that in the future the radiography of thyreoglossal fistulæ will be the first step in their investigation. A by-product of this clinical study may be a definitive description of the anatomy of the thyreoglossal tract, which has been the subject of differing accounts by different authors.

"BLACKOUT" IN THE AIR.

A good vocabulary of aeronautical words and phrases is today part of the equipment of every reader of the newspapers; many who are parents of small boys have even learned the meaning of some of these words and phrases. No one thinks that "flying blind" has anything to do with the consumption of alcohol by the pilot or that his eyes are covered, and only the "dear old ladies" beloved of comic journals might imagine that the feat was in any way associated with "blackouts". But stay, what of this word "blackout"? We have all heard it in the consulting room, and its meaning there is plain; for example: "As soon as I get out of bed and stand up I seem to have a 'blackout', doctor." Then there is the new kind of "blackout" whereby the night lights of towns and cities are doused or concealed from aircraft. *Punch* recently alluded to both these types of "blackout" in a single verse:

> I've covered Cook's skylight with heavy blue paint
> (She began it herself but she came over faint), . . .

We now encounter the word in a third, aeronautical sense, which is new to us, in an article by Wing-Commander P. C. Livingston on the problem in aviation of "blackout", a brief loss of vision affecting pilot or crew when an aircraft is made to turn in the air suddenly and at high speed.[1] This brief loss of vision has been called *Schwarzsehen* in the German literature, and Livingston also refers to it by the name of *amaurosis fugax*. It engaged the attention of the Royal Air Force medical authorities at the times of the Schneider Trophy races, as it constituted a danger when it occurred at low altitudes. The symptom was found to vary considerably in different persons; but members of the competing teams subsequently admitted that they minimized their sensations before the medical authorities in their zeal to fly in the race. In 1938 Livingston, with Flight-Lieutenant H. G. Lee, using a specially rigged Hawker-Hart aeroplane, made an experimental study of "blackout". By looping from a dive at 170 to 185 miles an hour it was shown mechanically that a force was exerted on the body equal to six times the force of gravity and was sustained for several seconds; by banking out of a dive at 160 miles an hour and turning round and round, a force equal to four times the force of gravity could be exerted on the body for fifty seconds or more. The great strains set up by these evolutions were reflected in stretching of the flying wires of the aeroplane, which in ordinary flying does not occur. It was shown that the susceptibility of the experimenters to "blackout" was dependent not only on the force applied to the body but on the time during which it was maintained; for instance, a force of 4·5*g* (where *g* is the force of gravity), if maintained for 15 seconds may sometimes produce the effect, while a greater force, say of 6·5*g*, kept up for only three or four seconds will not do so. Therefore "blackout" is more likely to make its appearance during sharp turns than after loops, for looping produces a very rapid falling off of speed and centrifugal force after the initial stress.

Describing his own experience, Livingston states that the first impression derived from the impact of the aircraft against the resistance of the air at the point of turn is one of intense bodily strain, producing a "concertina sensation". The cranium feels as though it were a solid ball of great weight, resting upon a feeble, compressible spinal column. The skin of the forehead, cheeks and eyelids has a feeling of numbness, which he likens to the sensation of an urticarial wheal. Then the visual disturbances make their appearance, usually in the form of a prodromal blurring or blue haze, followed rapidly by a sensation of intense blackness. In his own case the blindness came with such suddenness that warning signs were almost absent. Vision returned with similar suddenness; the wall of blackness "snapped away as does a camera shutter on its release". "Blackout" endures for from one or two seconds to twelve or twenty seconds. In the longer periods there seems to occur a state in which voluntary action is checked and thought is stilled.

According to Livingston "it is clear that all this symptom complex is the result of the blood supply to the brain being centrifuged away". Nevertheless it is far from clear. Admirable as is Livingston's consideration of the theoretical effects of centrifugal force on the circulation in various parts of the visual organs, pathways and centres, it is lacking in that it makes no reference to the part that might be played by diminution of the venous return to the heart and reduced cardiac output in the alteration to the intracranial circulation. Why the vision should be affected so much more dramatically than the other faculties is still an unsolved problem.

Research is now being directed to the discovery of means to combat "blackout". Airmen have found that by bending the body sharply forward at the moment of turn they are able to lessen the effects of the great stresses to which they are subjected. Special "oleo seats", which act as shock absorbers, and various types of belts of elastic webbing fitting about the abdomen directly upon the skin and so designed as to direct presure upwards as well as backwards, have also been found to increase the ability to withstand the effects of the forces exerted on the body during aerobatics.

[1] *The British Journal of Surgery*, July, 1939.

Abstracts from Current Medical Literature.

MEDICINE.

Transfusion Rendered Impossible by Sulphonamide Treatment.

G. A. SCOTT AND O. MEERAPFEL (*The Lancet*, July 29, 1939) report two cases in which treatment with a sulphonamide over a long period was followed by an alteration in the blood serum which precluded the finding of a suitable donor for blood transfusion. They also found that normal serum treated *in vitro* with a sulphonamide for four days or more agglutinated the red blood corpuscles of donors of the corresponding blood groups and those of universal donors.

Renal Infection.

HUGH CABOT AND T. R. MONTGOMERY (*New York State Journal of Medicine*, April 15, 1939) point out that there are a number of subacute inflammatory conditions of the kidney that heal frequently without surgical assistance. Massive abscesses or carbuncle of the kidney and the more common perinephric abscess, on the other hand, are essentially surgical problems. Today the diagnosis of a blood-borne infection of the kidney can be made accurately in the vast majority of cases if the possibility is thought of. In as many as 60% of the cases peripheral infection, such as a furuncle, a carbuncle or an infected wound, is evident. In another 20% a recent acute infection of the upper part of the respiratory tract appears to be the origin. Pain over the lower ribs is present in the majority of cases and may often be associated with chill and fever, thus suggesting a diagnosis of pneumonia rather than a renal lesion. Leucocytosis of a relatively high grade is the rule rather than the exception. Physical examination of the chest may often reveal vague dulness over the base of one lung, and even an occasional râle may be heard in the very early days. The examination of the abdomen generally reveals no abnormality and the urine is usually normal. Such cases are essentially pyrexias of unknown origin, and if the possibility of renal blood stream infection is thought of, the necessary confirming investigation can be carried out. During the first four or five days staphylococci can almost invariably be found in the urine if a smear is made from a specimen that has been centrifuged for half an hour at high speed. No organisms are cultured. This may be due to the failure to select the right medium or to the organism's being too feeble to grow. The excretion urogram may give positive evidence, not of deformity but of diminished, irregular, or occasionally absent excretion on the affected side. In the early stages there is some degree of perinephritis, which can be determined by the limitation of normal motility of one kidney as compared with its fellow. This can be determined during the course of the urogram if skiagrams are taken from various aspects. The normal kidney should have a motility roughly equal to the vertical diameter of one of the patient's lumbar vertebræ. After the lapse of a few weeks the retrograde pyelogram gives valuable diagnostic information; it will regularly show massive abscesses, and other abnormalities of calyces will be evident. Other evidence of perinephritic suppuration will by this time be present. Treatment depends on the ability of the patient to deal with his infection. It is necessarily supportive in the earlier stages and surgical in the advanced condition of extensive suppuration.

Thyreoid Extract and Heart Block.

M. AISNER AND J. F. DORSEY (*The New England Journal of Medicine*, August 31, 1939) report a case of complete heart block resulting from excessive dosage of thyreoid extract, which had induced a state of hyperthyreoidism. The patient was a woman, aged thirty-three years. Upon admission to hospital she was suffering from vomiting and diarrhœa. Examination revealed a well-developed and well-nourished woman, apprehensive, restless, at times hysterical, begging for water, which she would immediately vomit. There was a fine tremor of the hands and tongue, but there were no abnormal ocular signs; the remaining clinical signs were normal, except for a pulse and heart rate of 32 beats per minute. The urine contained a trace of albumin and a few red and white blood cells, whereas the blood picture showed a symptomatic anæmia with a neutrophilia, the leucocytes numbering 25,600 per cubic millimetre. An attempt was made to diminish the vomiting and diarrhœa. The pulse rate remained at an average of 30 beats per minute, and the electrocardiographic investigation showed the presence of "complete heart block with myocardial disease". The patient experienced short periods of apnœa associated with convulsive seizures lasting ten to fifteen seconds. In a few days there occurred a period of thirty-six hours of anuria. After reestablishment of the renal function signs of bronchopneumonia supervened at the base of the left lung, whereupon the pulse rhythm became regular at the rate of 88 per minute, and an electrocardiographic record was interpreted as being "within normal limits". During the phase of anuria the blood non-protein nitrogen value rose to 150 milligrammes per 100 cubic centimetres; but this gradually fell again. The pneumonic signs and symptoms subsided, so that after twenty-three days of illness the patient left her bed. She was discharged from hospital ten days later, quite well, the basal metabolic rate being −18%, the blood cholesterol value 147 milligrammes per 100 cubic centimetres, and the electrocardiogram normal. The authors state that a review of the literature since 1882 reveals a total of ten cases of complete heart block appearing during the course of true hyperthyreoidism, but no case such as this, in which the block was induced by the administration of thyreoid extract. In this case the patient had been advised three years prior to her admission to hospital to take thyreoid extract because of obesity associated with a low basal metabolic rate, and she had continued to take thyreoid extract intermittently and indiscriminately without supervision, so that during the five weeks prior to her illness she had taken from 12 to 15 grains daily. The authors discuss the factors involved in the pathogenesis of complete heart block in hyperthyreoidism, and remark that the transient nature of the block in the case reported suggests that it may be a function of reversible chemical changes in the myocardium rather than of morphological alterations. They report their case to illustrate what may be expected from the uncontrolled use of thyreoid extract in the treatment of obesity.

Chronic Rheumatism.

J. W. SHACKLE (*The Practitioner*, September, 1939) discusses the laboratory investigations in chronic rheumatism. He expresses the opinion that infection probably does play some part in many rheumatic conditions, and therefore it is wise to attack any possible foci, the most obvious of which are the teeth, tonsils and antra. The author has not been able to establish any constant findings in the bacteriological examination of the stools, gall-bladder contents and urine in these cases, nor does he consider the available evidence incriminating streptococci as a cause of rheumatic conditions to be strong. In a discussion of the biochemical examination of the blood in these cases he states that the blood sedimentation rate depends not upon an infective process as such, but upon the presence of an inflammatory process or of some material tissue damage. He illustrates this assertion by the greatly increased rates obtained in acute exacerbations of gout, in which disease no one has suggested an infective ætiology. Increase in the blood sedimentation rate has been found in rheumatoid arthritis, infective arthritis and acute gout, but not in muscular rheumatism or fibrositis. The author states that, helpful as the blood sedimentation rate is in diagnosis, it is even more valuable as a guide to prognosis, and that in his own series of cases of rheumatoid arthritis the patients with a rate greater than 50 millimetres in the first hour had a bad prognosis. The author has found a mild degree of secondary anæmia to be a common feature of patients with rheumatism. He has noted little variation from the normal values of the blood calcium, despite the extraordinary degree of rarefaction of the bones noted in skiagrams of

patients suffering from rheumatoid arthritis. He has observed a lack of uniformity in the values of the blood inorganic phosphates; but he considers the estimation of the blood uric acid level to be a valuable diagnostic and prognostic aid. He emphasizes the fact that the normal values of the blood uric acid are 3·0 to 3·8 milligrammes per 100 cubic centimetres of blood in a man, and 2·0 to 3·3 milligrammes per 100 cubic centimetres in a woman. He also confirms the findings of others in regard to glucose metabolism in rheumatoid arthritis, the glucose tolerance curve rising from normal values to a sharp peak, as high as 300 milligrammes per 100 cubic centimetres, and returning to normal rapidly in two and a quarter hours, the renal threshold for glucose being raised. There is usually no more than a trace of sugar in the urine, even when the curve is at its highest.

Myocardial Infarction without Coronary Lesions.

H. GROSS AND W. H. STERNBERG (*Archives of Internal Medicine*, August, 1939) report a study of fifteen cases of myocardial infarction without demonstrable occlusion of the coronary arteries. The blood pressure had been raised in thirteen cases. It was thought probable that extreme coronary vasoconstriction had produced the ischæmia leading to the infarction.

Hypertension.

B. A. HOUSSAY, B. MENENDEZ, J. C. FASCIOLO AND A. C. TAQUINI (*La Presse Médicale*, May 27, 1939) discuss the hypertensive action of the ischæmic kidney. They found that intense arterial hypertension could be produced in three ways: by section of the presso-receptor nerves of Cyon and Hering, by the suboccipital injection of kaolin, producing internal hydrocephalus, and by renal ischæmia. The production of partial renal ischæmia by progressive narrowing of the calibre of the renal artery in one or both kidneys caused permanent hypertension in the dog. This has been shown to be due not to uræmia or nervous reflexes, but to some substance in the kidney that has been found in the blood of the renal vein. This substance is a secretion, which on injection into other animals causes pronounced vasoconstriction; it does not pass through the ultra-filters. Asphyxia in a normal dog for four minutes produces this vasoconstrictor substance in the renal veins. It does not appear after excitation of the renal or great splanchnic nerves, nor in hypertension following section of the vagus nerves or the carotid nerves. If the renal artery was clamped so as to cause total ischæmia for six hours and then the clamp was removed, the blood that flowed through the kidney contained a hypertensive substance. The normal kidney tissue possesses a protective action, which either eliminates or destroys the vasoconstrictor substance. This substance acts independently of the suprarenals and its action is direct. Recently, reports of hypertension in man, associated with vascular lesions of the kidney with ischæmia, have been published. Patients suffering from hypertension have been cured by extirpation of a kidney of which the renal artery was narrowed, the other kidney being healthy. Finally, hypertension in dogs has been cured by the establishment of a collateral circulation for the kidney, by removal of its capsule and placing it in close contact with the mesentery and the spleen.

Crystalline Insulin.

A. CHOAY AND R. NETTER (*La Presse Médicale*, May 3, 1939) publish photographs of crystals of zinc, nickel and cobalt insulates. Insulin was first obtained in crystalline form by Abel in 1926. Scott and Fisher later showed the importance of zinc in the crystallization of insulin. Normally, zinc, nickel and cobalt were present in the pancreas. In the complete absence of zinc, insulin did not crystallize. If a small quantity of zinc, nickel or cobalt was added, crystallization occurred readily. Purified insulin from ox pancreas, in the presence of zinc chloride, began to crystallize in a few minutes, and crystallization was complete in some hours; the process could be watched under the microscope. Several successive crystallizations produced a constant product, containing 22 international units per milligramme. The crystals were colourless and had the appearance of precious stones until they were dried.

Oxygen in the Treatment of Coronary Thrombosis.

E. P. POULTON (*The Lancet*, August 5, 1939) believes that oxygen is the most valuable agent for the treatment of coronary thrombosis, improving the heart's action and giving relief from pain. He reports two cases in which the administration of oxygen by means of an air-tight tent was beneficial. He suggests and produces some evidence to show that patients suffering from other diseases in which there is local tissue anoxia, such as ulcer of the leg, cerebral thrombosis, and rheumatic myocarditis, might also benefit from treatment with oxygen.

Testosterone Propionate in Peripheral Vascular Disease.

EDWARD A. EDWARDS (*The New England Journal of Medicine*, May 25, 1939) gives a preliminary report on the results of the administration of testosterone propionate to seven male patients, three of whom were suffering from Buerger's disease and four from arteriosclerosis. In all cases there was involvement of the popliteal and femoral arteries. The absence of pulsation was confirmed by the use of a Pachon oscillometer. Testosterone propionate was given by intramuscular injection two or three times a week. No other treatment was given. Considerable subjective and objective improvement occurred; but the observations were made over several months only. The night pain was greatly ameliorated. Delay or abolition of intermittent claudication occurred. All patients reported an increase in activity and a feeling of optimism. These results are similar to those reported previously after treatment with this male hormone. The authors suggest a further trial to establish clearly its mode of action and to prove or disprove its harmlessness; it also remains to be seen whether its effect will vary in patients with or without testicular deficiency. Its usefulness in women is as yet undetermined.

Androgens in the Urine in Basophilism.

A. C. CROOKE AND R. K. CALLOW (*The Quarterly Journal of Medicine*, July, 1939) assert that the determination of androgens (17-ketosteroids) in the urine, which can be made by a rapid colorimetric method, gives valuable assistance in determining the presence of suprarenal cortical tumours in persons with basophilism. Their view is supported by detailed reports of four patients exhibiting basophilism, two of whom had suprarenal tumours and two not.

The Treatment of Chronic Hypoparathyreoidism.

E. ROSE AND F. W. SUNDERMAN (*Archives of Internal Medicine*, August, 1939) have treated five patients suffering from parathyreoid deficiency after thyreoidectomy by the oral administration of dihydrotachysterol in sesame oil. Dihydrotachysterol is a derivative of tachysterol, which is one of several sterols derived from ergosterol by irradiation with ultra-violet rays. It relieved the symptoms in a few days, and the serum calcium value soon returned to normal. It was found that excessive doses were capable of producing hypercalcæmia and symptoms of intoxication.

Myasthenia Gravis.

A. M. MINOT, K. DODD AND S. SKIVEN (*The Journal of the American Medical Association*, August 12, 1939) describe the effect of guanidine hydrochloride on seven patients with *myasthenia gravis*. A 2% solution given orally or intravenously in doses of 10 milligrammes per kilogram of body weight at a single dose, and repeated until 30 or 40 milligrammes had been given, improved the condition of the majority of these patients in every way. In some cases it was necessary to give prostigmin as well. Patients with *myasthenia gravis* tolerated larger doses of guanidine hydrochloride than normal persons, though in both gastro-intestinal symptoms, anorexia, vomiting, nausea or diarrhœa occurred. These symptoms appeared when the content in the blood was 0·5 to 0·6 milligramme per 100 cubic centimetres, as compared with the normal level of 0·35 to 0·45 milligramme. Further studies are in progress.

Special Articles on War Medicine and Surgery.

II.

ANÆSTHESIA IN RELATION TO WAR CONDITIONS.

ANÆSTHESIA, like all branches of medicine, has shown great advances since the Great War. These advances are to be observed not only in (i) the new drugs and gases used for and in connexion with anæsthesia, (ii) the elaborate anæsthetic apparatus, (iii) the complex anæsthetic techniques, but also in the special measures now adopted to increase the safety of surgical procedures, such as (*a*) preoperative investigation and preparation, and (*b*) the recording during operation of blood pressure and pulse rate.

Finally, mention must be made of the laboratory and clinical investigations which have thrown more light on the mode of action of anæsthetic drugs, their effects on the physiology of the body as a whole, and their influence in aggravating or limiting the effects of various pathological states.

There would appear to be great scope for the application of many of these developments in anæsthesia to war-wound surgery, complicated as it is by various pathological states and regional injuries, which may profoundly influence or be influenced by anæsthesia. However, before passing on to the consideration of the practice of anæsthesia for surgical therapy in the wounded, it would be relevant to consider the organization of and provision for anæsthesia necessary during times of war.

In modern warfare, surgical therapy and anæsthesia will be required not only for the wounded of the fighting forces but also for civilians, perhaps far from the scene of actual hostilities.

A full account of the organization necessary for an efficient and adequate anæsthetic service during war time would therefore embrace that required for (*a*) the fighting forces, (*b*) the civilian population.

THE CIVILIAN POPULATION.

The surgical and anæsthetic services for casualties amongst civilians would most probably be those already available in the established hospitals, unless, of course, the town or city should be devastated by enemy action, as has recently occurred in Poland. Such hospitals might have to be supplemented by the establishment of emergency hospitals, and these services would accordingly have to be augmented. The factors determining the choice and management of anæsthesia for such casualties will be very much the same as those operating for the wounded of the fighting forces and will be dealt with later. However, there should be more facilities for employing special anæsthetic methods.

FIGHTING FORCES.

Even in "the dark backward and abysm of time" the production of unconsciousness and analgesia in soldiers was contemplated, for it is stated in Homer's "Odyssey" that "Helen dropped into the wine of which the soldiers drank, a drug, an antidote to grief and pain, inducing oblivion to all ills".

Through the intervening centuries, with the changing character of warfare and the developments in the methods for the treatment of the wounded, the present medical organization has been built up for dealing with casualties amongst soldiers. It would be useful to consider the requirements of and the organization and facilities for anæsthesia in the field medical units and general hospitals of today (see Table I).

The arrangements for dealing with casualties in the field may vary somewnat under different conditions of warfare; but in general it may be stated that the following organization will be adopted.

IN ADVANCE OF THE CASUALTY CLEARING STATION.

In advance of the casualty clearing station the main object of the medical service is to collect and remove the wounded to the casualty clearing station quickly and in the best physical condition. The surgical possibilities are very limited and consist in the treatment of pressing surgical emergencies, such as the ligation of blood vessels,

TABLE I.

Requirements of and Provision for Anæsthesia in Field Medical Units and General Hospitals.

Unit.	Work Performed.	Requirements of Anæsthesia.	Equipment for Anæsthesia.
Field Ambulance.	Collection and evacuation of wounded; first-aid treatment; restorative therapy; grave and pressing surgical emergencies.	Primitive analgesia or nil (ligaturing blood vessels, amputations of shattered limbs, closure of open sucking chest wounds).	Chloroform or ether or perhaps intravenous.
Advanced Operating Unit.	Specialized surgical team (some conditions of warfare).	Specialized anæsthesia.	According to requirements of such a unit.
Casualty Clearing Station. (Mobile.)	Principal operating centre in forward zone; initial surgical treatment for bulk of wounded.	Every type of surgery in wounded with all types and grades of complicating factors; organized and specialized anæsthesia called for.	Ether: open masks, Flagg's can, Magill's tubes, laryngoscope. Chloroform: open mask, Junker's inhaler. Gas (N_2O): army model, complete with all attachments. Spinal: "Percaine". Intravenous: "Pentothal Sodium", "Evipan Sodium". Regional: "Planocain", "Novocain" 0·5% to 2·0%. Sedatives and analeptics, mouthgags and airways.
General Hospital. (Stationary.)	Principally surgery of election, much highly specialized.	As much of surgery is specialized and is for wounded with complicating factors, adequate organized specialized anæsthesia is required. As units are stationary, there is more scope for specialized anæsthesia.	The above *plus* an endotracheal machine. Basal narcotics (?). Gas machine with provision for cyclopropane.

the amputation of shattered or crushed limbs to facilitate transport, the splinting and extension of fractures and the closure of open sucking chest wounds. The requirements of anæsthesia and facilities for administering it are limited.

Frequently the loss or obtundation of the sense of pain, with or without loss of consciousness, resulting from the wound or from injection of morphine will permit of some of the surgical procedures being carried out without anæsthesia. In other cases light surgical anæsthesia or analgesia can be attained with chloroform or ether. In spite of certain undesirable qualities, no suitable substitute for chloroform appears to have been found for use under such conditions. It may be that one of the newer intravenously administered anæsthetics may prove a useful agent for the forward area.

In the Casualty Clearing Station.

In the field the casualty clearing station is the principal surgical unit and operating centre in the forward area. In this unit every type of surgery in wounded with all types and grades of complicating factors is carried out, and it is highly desirable to have a properly organized and well-equipped anæsthesia service developed here. An experienced and competent specialist anæsthetist will be in charge of the anæsthetists of the various surgical teams and his duties will comprise: (i) the administration of the anæsthesia service in the casualty clearing station; (ii) the supervision and training of the anæsthetists in the more specialized anæsthetic procedures; (iii) collaboration with the surgeons and physicians in pre-operative investigations (blood pressure estimations *et cetera*); (iv) supervision of and assistance with preoperative and post-operative treatment (blood transfusion, saline infusions, preoperative medication, oxygen therapy *et cetera*); (v) consultation with the surgeons as to (*a*) the optimum time to operate on the seriously wounded and (*b*) the most suitable anæsthetic agent and method to employ; (vi) supervision and training of nursing orderlies in pre-operative preparation and post-operative management of casualties.

When heavy fighting is in progress and casualties are pouring in, there should be, if possible, two anæsthetists to each surgical team, as in war surgery, even as it is in the surgery of civil practice, a large part of the time of an operation is taken up in the induction of anæsthesia, the cleaning up of the damaged parts, the application of splints and dressing and the transport of the patients to and from the theatre. With two operating tables and a well-trained team it should be possible for a surgeon to keep two anæsthetists fully occupied. Under these conditions it is estimated that an average of 1·5 to 2·0 patients can be operated on per hour.

Anæsthetic Equipment of a Casualty Clearing Station.

A certain scale of equipment for anæsthesia is laid down for a casualty clearing station; but this can be added to should it be found necessary to do so. If we bear in mind the conditions met with in the field, the following points must be considered when such equipment is being decided upon: (i) it must be standardized, because of the frequent and necessary changes in anæsthetists who will be called upon; (ii) it should be as simple as is compatible with efficiency; (iii) it should combine portability with strength and absence of perishable and fragile parts.

The following anæsthetic drugs and equipment should fill all the requirements in a casualty clearing station.

Ether.

Ether will be the main anæsthetic agent used in a casualty clearing station. For field conditions it would be best to put it up in copper-lined metal containers. The majority of administrations will be by the open method, for which suitable masks are provided. When it is necessary to use it for endotracheal anæsthesia, Flagg's can (see Figure I) with a large Magill's tube (permitting to-and-fro respiration to take place) will prove adequate and obviate the necessity of a special endotracheal machine. A laryngoscope of Magill's type, with cord and separate battery, will be available for intubation of the larynx.

Chloroform.

In spite of its growing disuse in civil practice, chloroform will be extensively used in the field, either by the open method or with a Junker's apparatus.

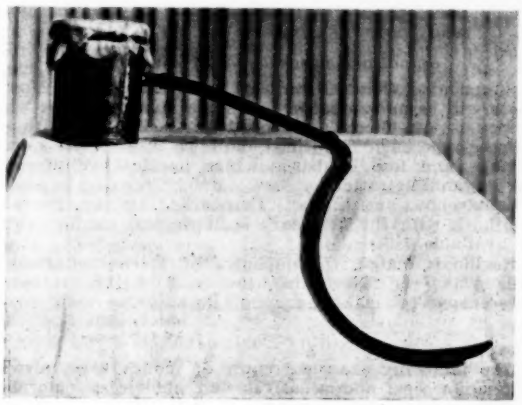

FIGURE I.
Flagg's can for endotracheal inhalational ether anæsthesia (Magill's tube attached)

Gas.

Nitrous oxide and oxygen will be required for certain types of wounded. A special field service unit (see Figure II) has been designed primarily for use in field hospitals. This unit is sufficiently robust to withstand

FIGURE II.
The "Austox" field service gas anæsthetic machine and case for carrying it.

the hard use it will encounter in service, yet is portable, light and compact. For transportation the entire machine is protected by means of a light steel cover, in the top of which is a felt-lined compartment, subdivided for the housing of the standard equipment. It may be used for continuous-flow administration or for carbon dioxide absorption by means of a modified Waters's soda-lime canister. The standard equipment supplied with the machine includes an ether vaporizer, soda-lime canister,

masks, exhalation valve, endotracheal adaptor, Magill's tubes (numbers 10, 8, 6) and laryngoscope (*vide supra*). This apparatus can also be used for endotracheal ether-oxygen anæsthesia in cases requiring lung inflation, which is impossible with Flagg's can.

The cylinders of gas supplied have a capacity of 100 gallons.

Spinal and other Types of Anæsthesia.

Spinal analgesia will be used in certain cases. Most of these will be mid-spinal or low spinal analgesias for which ampoules of "Percaine" solution (1 in 200 with 6% glucose-hyperbaric solution) will be used. A suitable syringe and fine lumbar-puncture needles are necessary for its administration.

Intravenous anæsthesia: "Evipan Sodium" or "Pentothal Sodium", with the necessary syringes and needles, should be available.

Regional analgesia: Ampoules of sterile solutions of "Planocain" or "Novocain" (0·5 to 2·0%), or tablets of these drugs for making up the solutions, are required.

Other Equipment.

The following are also required: mouth gags, airways, tongue forceps, and sedatives and analeptics (morphine, barbitone, "Coramine", ephedrine sulphate).

(Under some conditions of warfare an advanced operating unit is set up in advance of the casualty clearing station; such a unit may carry out some specialized form of surgical work, and in consequence will have attached to it an experienced and competent anæsthetist with suitable equipment.)

In General Hospitals in Rear of Casualty Clearing Station.

In general hospitals the surgical therapy will be usually surgery of election, and some of it will be highly specialized. This will call for specialized anæsthesia. These hospitals being stationary units, the organization and equipment for anæsthesia will provide greater scope for the employment of the developments and requirements of anæsthesia. A specialist anæsthetist will be in charge of the anæsthesia services and his duties will be similar to those of such a specialist in the large general civil hospitals.

Adequate equipment and agents would be available, such as for a casualty clearing station, with some additions, which surgery in these hospitals may call for; for example, cyclopropane and basal narcotics (paraldehyde or "Avertin").

Additional equipment will include: (*a*) anæsthetic machines for endotracheal anæsthesia; (*b*) a gas machine with provision for the administration of cyclopropane. Such provision could be met by the attachment of a flow meter for cyclopropane to the field service unit, or suitable machines could be obtained from civilian sources.

The main desiderata in the equipment of such hospitals are the standardization of apparatus, drugs and methods, and the elimination of personal preferences.

With this outline of the organization and equipment for anæsthesia in the field medical units and general hospitals the practice of anæsthesia in war-wound surgery can now be considered.

Anæsthesia in the Surgery of War Wounds.

As a basis for the discussion of anæsthesia for the wounded requiring surgical therapy it is necessary to divide them into three groups: (i) slightly wounded, with little or no evidence of any complicating factors; (ii) severely wounded with but slight evidence of any complicating factors; (iii) severely wounded with definite evidence of one or more complicating factors, such as pathological states (shock, hæmorrhage, infection, effects of chemical warfare) or regional injuries.

It will suffice to consider the question of anæsthesia in relation to groups (i) and (iii), as an understanding of the underlying principles in the anæsthesia of these extreme types of casualty should lead to an appreciation of the requirements for group (ii).

Slightly Wounded with Little or No Evidence of any Complicating Factors.

The majority of the slightly wounded men will receive the necessary initial surgical treatment in the casualty clearing station. Many of them will be unprepared for anæsthesia. They may have both the stomach and lower bowel full and in cold climates may be suffering from varying degrees of pulmonary infection. A proportion of this group of wounded will be in good physical condition. In this type of casualty the main desiderata from the anæsthetic point of view are safety, speed and convenience. The ideal anæsthesia is one in which induction is rapid and recovery complete a few minutes after operation and in which there is little risk of producing or aggravating any pulmonary infection. Under the conditions met with in the field, however, the ideal anæsthetic must often be sacrificed for the one that is most readily available. In consequence the following types, whilst not fulfilling all the requirements set forth above, will doubtless be used.

Nitrous Oxide and Oxygen:

Whilst nitrous oxide and oxygen mixture is apparently ideal from the point of view of rapidity of action and recovery, there are certain types of patient who are notoriously difficult to anæsthetize with this agent, because it has such a weak anæsthetic action. Many of this group of wounded will be in this category. If it is to be used for the anæsthetic-resistant types, its weak action has to be reinforced by reduction of the oxygen intake to levels where asphyxial signs appear and there is only a narrow margin of anæsthesia between response to a surgical stimulus and asphyxial spasm. An attempt to subdue a difficult patient (strong vigorous soldier) with nitrous oxide and oxygen alone, results in anoxæmic muscular spasm, which may make operative procedures requiring muscular relaxation difficult or impossible. Provided reflex response to stimuli does not prove an obstacle, analgesia and amnesia may suffice for some procedures and may be attained without the development of profound asphyxial signs.

In these resistant types of wounded nitrous oxide can be reinforced by a more powerful anæsthetic agent, which will permit of the introduction of additional oxygen to avoid the production of anoxæmic spasm; for example, ether or cyclopropane. The use of cyclopropane in these cases in the casualty clearing station seems neither desirable nor possible of achievement. Both these agents make the nitrous oxide and oxygen mixture explosive, and whilst ether delays the recovery from anæsthesia and may predispose to or aggravate any pulmonary infection, cyclopropane is expensive and requires additional apparatus for its administration and experienced anæsthetists to administer it.

The most useful adjuvant is probably one of the intravenously administered barbiturates. Usually 0·2 to 0·4 gramme will produce unconsciousness and then nitrous oxide and oxygen anæsthesia can be started. The recovery period is scarcely longer than with nitrous oxide and oxygen alone.

The principal objections to the use of nitrous oxide and oxygen anæsthesia for this type of wounded are that (i) with the limited number of gas machines available the operative treatment of more serious cases in which there are definite indications for its use may be held up; (ii) nitrous oxide and oxygen, which have to be transported in heavy cylinders, are used unnecessarily; (iii) an anæsthetist, competent in gas anæsthesia, must give the patient his close attention throughout the operation.

"Pentothal Sodium" and "Evipan Sodium".

"Pentothal Sodium" and "Evipan Sodium" combine all the desiderata for anæsthesia for this class of casualty (and even for the more severely wounded if suffering from the effects of chemical warfare). They will prove of inestimable value and should be on the scale of equipment. They are the most portable and least subject to damage in transport of all anæsthetics. The induction is rapid and quiet, and recovery the same, and nursing orderlies are

thereby freed from the duty of supervising recovery. They are non-irritating to the lungs and do not aggravate mild pulmonary infections or the effects of chemical warfare on the lungs.

These drugs can be repeated daily (for example, for painful dressings) without ill effects. They are non-inflammable and non-volatile.

The only apparatus required for their use is a syringe with a capacity of ten cubic centimetres and some needles, size 14, which can be sterilized beforehand or carried in a metal container immersed in spirits.

Mode of Administration.

These drugs can be administered by three methods: (i) By a single dose, a method of administration that is suitable only for short procedures (five to fifteen minutes); the drug can thus be given by the surgeon. (ii) By intermittent dose, the needle being left in the vein and the anæsthetic solution injected, after consciousness is lost, in amounts of 0·5 to 1·0 cubic centimetre, as required; anæsthesia of 20 to 40 minutes is available. (iii) By continuous dose, a method requiring additional apparatus, combining the continuous-drip administration of saline solution with that of anæsthetic solution which is added as required. This permits of prolonged anæsthesia, up to one or one and a half hours; but the patient remains very drowsy after this dosage.

Points to be Stressed.

After an experience of the use of these drugs in several thousand cases in civil practice the following points are stressed: (i) they should be administered in small doses, which can be added to as is required; (ii) in resistant individuals the uncertainty of their effects can be overcome by their more rapid injection; (iii) absolute patency of the airway must be maintained, the reduction in the minute volume respiration demanding excessive care of the airway, otherwise anoxæmia may develop; (iv) operative measures in the oral cavity or about the pharynx or larynx predispose to the development of severe laryngeal spasm, which, if associated with the accumulation of much blood in the posterior part of the pharynx, may lead to an alarming train of events.

The contraindications to the use of these drugs for this type of wounded are hepatic, cardiac or pulmonary insufficiency, which is not likely to be met with.

In carrying out surgical procedures in large numbers of cases, 40 to 50 cubic centimetres can be made up at a time in a sterile flask and enough poured out into a medicine glass for each case. In such circumstances a tremendous amount of time can be saved by the use of these drugs. When "Pentothal Sodium" is used care must be taken to avoid injecting it outside the vein, because it is very irritating to the tissues and will cause extensive sloughing.

Simple as their administration may seem, it should be remembered that their safe and satisfactory use, particularly for prolonged anæsthesia, demands skill and experience.

Ether.

Although ether does not comply with the desiderata laid down for the anæsthesia of the slightly wounded, its immediate safety and certain action and the simplicity of its administration will probably result in its being the most universally employed anæsthetic agent. Its volatility may preclude its use in the tropics. In cold climates or in the anæsthesia of gassed and wounded men its use may predispose to pulmonary complications and it would therefore be better to avoid it.

Chloroform.

The great value of chloroform for the production of anæsthesia in this type of wounded is agreed upon by many of those who have had experience of its use on service. It is certain in its action, even on strong vigorous soldiers, is more pleasant to take, and does not produce the sense of suffocation during induction that occurs with ether. It was the experience of many of those who used it in the Great War that those undesirable effects which are occasionally met with in civil practice were rarely met with in slightly wounded soldiers, who, apart from their wounds, were usually in good physical condition. Other competent and experienced anæsthetists assert that its routine use even for slightly wounded is to be condemned. Silk[10] believes that the mortality among wounded anæsthetized by chloroform, even when it is skilfully administered, is 1 in 2,000. He states that from January, 1917, until the time of writing his paper (March, 1918) at least 55% of deaths during anæsthesia were due to, or occurred under, chloroform used in an undiluted form, and in fully 28% of this 55%, death occurred before the operation had started. In many of these cases the use of chloroform was obligatory, and in a small percentage of cases death would have occurred whatever the anæsthetic. He advocates its dilution with ether in the form of one of the numerous chloroform-ether mixtures. This is used for induction prior to ether alone.

Unless the newer intravenously administered barbiturates prove their value for this class of casualty, chloroform will continue to be largely employed. In the tropics and in cold climates and for the gassed wounded it has advantages over ether.

Regional Analgesia.

Regional anæsthesia will probably prove invaluable for many of those who have small wounds which require excision and who have also been gassed. Besides its particular advantages in this type of case it may prove useful because the surgeon can give it himself and the patient retains consciousness the whole time. However, rather more time will be taken up with this method.

Spinal Analgesia.

In the more severely wounded of group (i) and perhaps group (ii), in whom there is no evidence of shock, but who may be suffering from the effects of chemical warfare, spinal anæsthesia would be suitable for operations on the lower limbs, for example, multiple excision of wounds.

Severely Wounded with Evidence of Complicating Factors, such as Pathological States (Shock, Hæmorrhage, Infection, Effects of Chemical Warfare) and Certain Regional Injuries.

The great bulk of the surgical therapy for the wounded of group (iii) will be carried out at the casualty clearing station, where facilities are available for appropriate pre-operative preparation and treatment, and where ample equipment and trained personnel should be available for the carrying out of the specialized anæsthesia which is so vital for this type of wounded.

Influence of Complications.

These wounded, having been exposed for some hours, perhaps in the wet and cold, and having had to be transported by hand stretcher and motor ambulance over indifferent roads, in spite of having received restorative and supportive treatment, may arrive at the casualty clearing station still suffering from the effects of shock and hæmorrhage and perhaps already developing signs of infection or showing evidence of the effects of chemical warfare. As surgical treatment may have to be carried out at the earliest possible moment, it is apparent that great judgement will be necessary as to the optimum time to operate and the most suitable form of anæsthesia to employ. The complicating factors (pathological states or regional injuries or both) must be borne in mind when a decision on these points is being made. These various complicating factors may occur singly or together in various combinations; but for their consideration in relation to anæsthesia for the severely wounded it will be satisfactory to discuss them under four headings.

Hæmorrhage and Shock.

The signs, symptoms and management of the shock-hæmorrhage syndrome have been dealt with in other lectures. Actually, from the point of view of anæsthesia,

no useful purpose is served by an attempt to draw fine distinctions between the two conditions, because in a patient suffering from either or both there is a definite reduction not only in the oxygen-carrying capacity of the blood but also in the efficiency of the circulatory mechanism, and tissue anoxia in varying degrees will be present. These important facts must be borne in mind when anæsthesia of wounded showing evidence of shock or hæmorrhage is being contemplated or actually carried out. It has long been recognized as unwise to operate on a patient suffering from severe shock, and it is advisable that anæsthesia and surgical intervention be delayed until a favourable reaction has taken place. Whilst this holds for well-established secondary wound shock, it is asserted that[3] if the severely wounded can be operated on before shock develops, much better results will be obtained.

The optimum time at which operation under anæsthesia should be carried out will require careful judgement and can only be decided after close watching and investigation of the patient by the surgeon and anæsthetist. The charting of the pulse rate and blood pressure is of inestimable value in this regard. From the practical point of view a systolic pressure of 80 millimetres of mercury or lower, if not raised within four hours, will have a fatal result. To attempt to anæsthetize a patient in this condition and add to the existing shock the shock of the operation is to court certain disaster. In some cases, such as open sucking wounds of the chest, the only hope of saving the patient is by immediate operation, and this risk must be taken. Where the urgency is not so extreme, appropriate restorative treatment is carried out, and as the blood pressure rises and the optimum period of improvement is reached, a decision as to the time to operate can be made. Too great delay, however, may predispose to the development of other complicating factors, such as infection (gas gangrene).

Infection.

The toxæmia of rapidly advancing infection in these cases will add its quota to the profound circulatory depression and may call for early appropriate surgical treatment. Infection with *Bacillus tetani* may progress to the point of tetanic spasms. These lead to ultimate death by producing spasm of the diaphragm, exhaustion from want of sleep and inability to take food. The tetanic spasms are best controlled by "Avertin" given *per rectum* in full doses. "Avertin" controls the spasms for periods up to six hours, during which time the patient rests and food can be given. The "Avertin" can be repeated every six or seven hours for several days.

Effects of Chemical Warfare.

From the point of view of anæsthesia the effects of the vesicant and suffocating gases are of importance because of their effects on the respiratory tree. These agents used in chemical warfare produce congestion and œdema of the respiratory passages and alveoli, and may ultimately lead to pulmonary consolidation. As a result gaseous interchange is interfered with and anoxæmia leads to death.

In the wounded who have been gassed great care must be exercised in the type of anæsthetic agent used, for fear of aggravating the lesions in the respiratory tract (*vide infra*).

Regional Injuries.

Some regional injuries will have a profound influence on the type of anæsthesia employed (*vide infra*).

Preoperative Preparation.

Preoperative measures will include appropriate treatment for the complicating pathological effects (shock, hæmorrhage, infection) of chemical warfare.

Preoperative Medication.

Morphine: Morphine should be given in most cases of shock; for in order to conserve the patient's energy and reduce the oxygen requirements of the tissues it is necessary to relieve pain and lessen anxiety and restlessness. Marshall,[3] who had a wide experience as an anæsthetist in a casualty clearing station during the last war, states that it should be used with some care when operation is contemplated. It is his opinion that the severely wounded do not make good recoveries from operation if given large doses of morphine just before operation. Used before nitrous oxide and oxygen anæsthesia, it certainly augments its weak anæsthetic effect.

Barbiturates: Weddell and a committee of the Council of the Royal College of Surgeons[4] are agreed that the employment of the barbiturates for patients already in a condition of shock is definitely dangerous.

Anæsthetic Agents.

It will be obvious from the foregoing remarks that it is impossible to lay down hard and fast rules for the type of anæsthesia for this group of wounded. Each case must be considered individually. In the casualty clearing station particularly, even in this group of wounded, it may happen that the ideal anæsthetic will have to be replaced by the one that is available.

In a consideration of the various anæsthetic agents which are likely to be used, stress will be laid on their advantages and disadvantages for the different conditions complicating this group of severely wounded.

Nitrous Oxide.

The consensus of opinion of those who had to undertake the treatment of wounded in the last war is that nitrous oxide is the most suitable anæsthetic for the seriously wounded, particularly those suffering from shock and hæmorrhage. The virtues of nitrous oxide in these cases are: (*a*) its weak anæsthetic action, (*b*) the absence of any effect on the chemistry of the tissue cells and fluids, (*c*) the absence of any action on the renal or hepatic function, (*d*) the absence of any irritative effect on the respiratory tract, (*e*) the rapid recovery period.

The only untoward effects likely to result from the use of nitrous oxide are due to inadequate oxygen in the nitrous oxide and oxygen mixture. In the wounded with circulatory depression resulting from shock, hæmorrhage or infection, any undue reduction of oxygen in the inspired air may determine a fatal issue, so that this anæsthetic agent, which is so valuable, has potential dangers in the hands of the inexpert or inexperienced. In many of the seriously wounded with shock, the consciousness is already dulled and the sensitivity lessened, and nitrous oxide would appear to produce complete unconsciousness and analgesia even in the presence of percentages of oxygen as high as 15% to 18%. Such amounts of oxygen would, of course, not produce even loss of consciousness in wounded in good physical condition. Even in the wounded with severe shock, muscular relaxation and abolition of reflexes is not to be expected, and will be rarely attained, nor will they always be necessary.

The following points should be borne in mind when anæsthesia with nitrous oxide and oxygen is being used for those wounded with signs of shock and hæmorrhage.

1. Adequate oxygenation must always be maintained. If consciousness cannot be completely abolished or reflex activity adequately controlled, ether or cyclopropane (if available) should be added rather than that these patients should be subjected to the risk of anoxæmia.

2. In profound anæmia, anoxæmia may occur without cyanosis because there is insufficient reduced hæmoglobin to produce cyanosis.

3. An anæsthetic machine should be employed which is capable of giving accurate mixtures of nitrous oxide and oxygen and provides for rapid inflation of the lungs with oxygen.

4. Where adequate muscular relaxation is required, as in laparotomies and perhaps thoracotomies, ether should be added in minimal amounts as a supplement. In the general hospitals cyclopropane may be available for this purpose. It is far more potent than nitrous oxide and can be given with 80% to 85% of oxygen. If obtainable, it will be found ideal for certain conditions that would be met with in the general hospitals, such as reamputations in wounded

suffering from the effects of war gas or infection, operations on casualties with profound sepsis or thoracic surgery with complications due to wounds or effects of gas.

Ether.

Although not the ideal anæsthetic agent for this group of wounded, ether will on occasions doubtless be the anæsthetic of necessity. When it has to be employed in shock or hæmorrhage it should be given in minimal amounts, for small amounts in such cases will provide adequate anæsthesia. The condition of those suffering from wound shock often appears to improve under ether anæsthesia, but an hour or two later it will show a pronounced deterioration.

In some of these cases it will suffice to produce analgesia and abolish consciousness (as is developed at the end of the first stage of anæsthesia). This can be achieved with very little ether, and where slight reflex response to stimulation does not matter, will prove sufficient for some procedures.

When exploration of the abdomen has to be made, the more adequate relaxation available with ether alone or with ether as a supplement to nitrous oxide and oxygen will permit of better exposure and in consequence more thorough and more rapid operative manipulations. Its employment as a supplement to nitrous oxide and oxygen has already been mentioned. Its use with carbon dioxide absorption results in warming of the inhaled air and retention of the water vapour.

During the Great War the use of warmed ether vapour was strongly advocated. Apart from facilitating the vaporization of the ether, there is no inherent advantage in this method. Whether it is warmed or not, it reaches the alveoli at body temperature. The amount used is about the same.

Chloroform.

Chloroform is a quite unsuitable anæsthetic for this type of wounded; but doubtless on occasions it will have to be used. Like ether, it should be given in minimal amounts for the shortest possible period. Generally speaking, if it is used for prolonged deep anæsthesia in shocked patients it will cause death of the patient, either immediately, from its profound depressant effect on the circulatory mechanism, or, later, from the effects of liver damage, predisposed to and exaggerated by the tissue anoxia. Jarman[5] states:

> . . . during the last war it was noticed that chloroform anæsthesia was unsuitable for wounded suffering from shock. Although the favourite anæsthetic of the uninitiated, being portable and easy to administer, the mortality under chloroform for amputations through the upper half of the thigh was over 90% in the C.C.S. The mortality under gas and oxygen was reduced to less than half this figure.

Spinal Analgesia.

In casualties with shock or circulatory depression from any other cause (for example, infection, effects of chemical warfare) spinal anæsthesia is definitely dangerous. This opinion is expressed by a committee from the Council of the Royal College of Surgeons.[4]

Marshall,[3] who during the last war carried out investigations on the use of spinal analgesia for surgical therapy in wounds of the lower extremities, is of the opinion that it is only suitable for patients requiring operation on the lower extremities if they have been wounded not less than forty hours before operation, unless it has been shown that their blood is of normal concentration. There will be undoubtedly a group of wounded (for example, group (ii), severely wounded, with only very slight evidence of complicating factors) for whom its use will be required. Adequate premedication to avoid psychical shock is advisable, and this can be supplemented with nitrous oxide and oxygen during the course of the operation.

As the majority of patients will require a low or mid-spinal analgesia, a hyperbaric anæsthetic solution, such as "Percaine" (1 in 200 with 6% glucose solution) will prove most useful.

On the assumption that wound shock is due to the bombardment of the higher centres by nociceptive impulses, some surgeons have advocated the use of spinal analgesia as a therapeutic and prophylactic measure for traumatic shock with severe injuries of the lower limbs. The clinical experiences of these men, as stated, conform with the results obtained by O'Shaughnessy and Slome[6] in their experimental work on traumatized cats.

Based on experience in the last war, and in civil practice, Reader[7] states that he has reached the following conclusions: (i) every patient with serious injury of the lower limbs should be given a spinal anæsthetic as the first and most important first-aid measure, after which splintage, restoration of warmth *et cetera* should be carried out; (ii) failing a spinal anæsthetic (or when this is inapplicable, such as in arm injuries), morphine should be given in full doses as the first anti-shock treatment.

Under war conditions there are, of course, obvious difficulties which will preclude its use early enough for it to be of great value.

The advocates of these methods of shock therapy maintain that if a patient is capable of recovering (for after a long period of barrage of the central nervous system the vital centres are irreparably exhausted), a spinal anæsthetic will raise the blood pressure and maintain it at a higher level, and this, combined with blood transfusion to replace the fluid loss, will give him his one and only chance.

Regional Analgesia.

Regional anæsthesia will have a definite sphere of usefulness in the treatment of patients with severe shock, who may also have pulmonary complications resulting from gas warfare. As with spinal analgesia, obtundation of consciousness by suitable premedication is advisable to avoid psychical shock. In the case of multiple wounds, unless a nerve block can cover the affected area, this method may be too time-consuming and require excessive amounts of anæsthetic solution. If regional infiltration is used, in addition to the toxic effects produced by the excessive amounts that may be required, the œdema resulting from the infiltration in the area of the wound favours the growth of organisms and retards healing. Nerve blocks may be possible; but it is difficult to foretell the exact extent of the operation.

In laparotomy local infiltration of the abdominal wall may provide muscular relaxation with nitrous oxide and oxygen anæsthesia, whereas this would be impossible with nitrous oxide and oxygen alone. Another advantage of this combination is that consciousness is abolished. Such a technique might be used when laparotomy was necessary in a gassed casualty when ether was contraindicated.

Further Considerations of Anæsthesia for the Gassed Wounded.

The question of anæsthesia of the gassed wounded has already been mentioned; but in view of the possibility of chemical agents being used more extensively in the present war, it would be advisable to consider it in more detail

At *La Conférence Chirurgicale Interalliée* (1918)[8] the following conclusions were arrived at on the question of anæsthesia for the gassed wounded.

1. Except in cases of absolute necessity it is wise to refrain from anæsthetizing wounded who have been gassed with the volatile hydrocarbons. In an emergency chloroform is to be preferred to ether.

2. Gas anæsthesia (nitrous oxide) is less harmful, but it has a weak anæsthetic action and the associated anoxæmia causes an increase in minute volume respiration and predisposes to pulmonary œdema.

3. Regional anæsthesia is the method of choice if the character and site of the wounds permit its employment. Multiple wounds or the alteration of the tissues by vesicants may preclude its use.

4. Spinal analgesia has a limited sphere of usefulness in the treatment of patients with wounds of the lower limbs who have suffered no fall in blood pressure.

Since the Great War the problem of anæsthesia for the gassed wounded has been extensively investigated. From

the literature it appears that the bulk of this investigation has been carried out by French and particularly German workers, which may or may not be of significance.

Cordier[9] has reviewed this work and his conclusions may be stated as follows.

1. Regional analgesia is the method of choice when it can be used.
2. Spinal analgesia will be reserved for those wounded requiring operations on the lower limbs, provided they show no fall in blood pressure.
3. If either of these methods is not possible, preference should be given to intravenous anæsthesia or "Avertin" narcosis. The former is preferred because of the simplicity of the technique. Experimental work carried out recently by Hecksteden[10] (Military Medical School of Berlin) points to intravenous anæsthesia as being highly satisfactory for gassed wounded. He suggests that small doses only may be required, and in some cases it may be wise to administer oxygen at the same time.
4. The use of cyclopropane for the gassed wounded has yet to be tried; but its inflammability, explosibility, cost and the more complicated apparatus necessary for its administration are obvious disadvantages which will limit its use in the field.
5. The volatile hydrocarbons should not be used for this type of wounded.

Some Regional Injuries and their Influence on the Choice of Anæsthesia.

The location and character of the wounds inflicted by the modern missiles of warfare are so multifarious that there is no tissue or organ which is immune to their lethal effects. On account of their anatomical situation or the physiological disturbances they engender, some of the wounds of special organs or regions, which require surgical treatment, will call for certain special forms of anæsthesia. In such casualties the regional factors will be the dominant ones in deciding upon the anæsthetic agent and method to be employed, and although the choice of the anæsthetic involves due consideration of other factors (*vide supra*) in general, it may be stated that the following types of anæsthesia will be adopted in the regional injuries to be mentioned.

Wounds of the Head.

As a result of the experience gained in the Great War and in the subsequent twenty years in civil practice it is recognized that the highly specialized surgery necessary in these cases is best performed by teams of specialists, which will include an anæsthetist.

Although there may be some variations in the methods of anæsthesia employed by the various surgeons, in general it is likely that the following will be used.

In the wounded who are quiet and controllable or unconscious, the necessary surgical treatment can be carried out under regional analgesia (either a field block or nerve block).

In those who are conscious, particularly if of a nervous temperament or restless, some form of sedation should be employed, such as morphine in a dose of one-sixteenth to one-quarter of a grain, or "Omnopon" (one-third to two-thirds of a grain), perhaps with scopolamine (one one-hundred-and-fiftieth of a grain) administered half to three-quarters of an hour before operation. For deeper sedation a basal narcotic should be given; for example, paraldehyde or "Avertin" in appropriate dosage.

Jefferson[11] recommends that a 1% solution of "Novocain", with five drops of adrenaline solution (1 in 1,000) to one ounce of the solution, should be injected under the galea until a wheal half an inch high is raised; at first it is so injected that the whole of the planned field is enclosed. Further injections can be made if the primary incisions need enlarging. Apart from the large meningeal vessels and the basal *dura mater*, the whole operation area will be thereby rendered insensitive. The temporal muscle should be liberally infiltrated if the operation field encroaches on this region.

In those wounded who are restless and uncontrollable it may be impossible to perform the necessary operation without a general anæsthetic. This may be supplemented by local infiltration of the scalp with "Novocain" and adrenaline to check the hæmorrhage. Ether, usually by the endotracheal route, with a large Magill's tube, will be the most frequently used general anæsthetic. It may be preceded by an appropriate dose of "Avertin".

Wounds of the Face and Jaw.

In wounds of the maxillo-facial region (including the mouth and lower jaw) the necessity for special anæsthetic methods is imperative. The character of the wounds in this region varies considerably; but it is safe to state that in only a few are the simple routine methods of anæsthesia applicable.

The chief difficulties arise from: (*a*) the presence of large quantities of blood and lacerated tissues in the mouth and pharynx; (*b*) the injured structures obstructing the upper air passages (*vide infra*); (*c*) the necessity for the anæsthetist to get out of the surgeon's way; (*d*) the technical difficulties in manipulating the anæsthetic in the presence of injuries. These difficulties are very real in wounds of the inside of the mouth, with or without involvement of the upper or lower jaw.

If the wounded with such injuries survive the immediate danger of suffocation due to loss of control of the tongue or of drowning in their own blood, great care should be taken that they are suitably postured during their transport back to the casualty clearing station. They should be placed on the stretcher in the prone position, with the head hanging downwards over the edge of the stretcher. The tongue must be kept forward in these cases, a procedure that not only preserves a patent airway but also tends to lessen hæmorrhage. Emergency tracheotomy in the forward area at advanced dressing stations or main dressing stations has been recommended for such cases. This procedure permits of the packing of the oral cavity with gauze, thereby checking hæmorrhage and facilitating subsequent anæsthesia. It is open to the objection that it may predispose to pulmonary infection.

In some cases of this type induction of anæsthesia may be effected with the patient lying semi-prone. Chloroform and ether will be the two agents most commonly employed, and they will be administered by the endotracheal route. Intubation can be performed under vision, blindly or digitally. If an endotracheal machine is available, the insufflational method may be used with ether. If such a machine is not available, just as satisfactory results are possible with the inhalational technique with a large-bore Magill's tube and a Flagg's can. To-and-fro respiration takes place along the large-bore tube, which may be regarded as a prolongation of the trachea. This simple method is not as well known in Australia as it should be. Provided the length of tubing between the catheter and the can is sufficiently wide and not too long (six to nine inches) no untoward results are possible. It has the great advantages that absolute patency of the airway is assured and that the entry of blood, mucus and foreign bodies (teeth or pieces of bone) is safeguarded against because the pharynx and aditus of the larynx can be completely packed off.

Another method which may be sometimes employed is the rectal oil-ether injection of Gwathmey. Of course this necessitates particular watch on the airway.

Provided care is taken of the airway, intravenous anæsthesia may serve in some of these cases. However, the laryngeal spasm which often accompanies the presence of blood and mucus in the pharynx, or operative intervention in this region, must be remembered and appropriate remedial measures for such a complication should be on hand.

Finally, gas-oxygen analgesia administered by a nasal face-piece, with the patient perhaps sitting up, was employed during the last war for some of the operative procedures in and around the mouth.

Silk used oxygen with chloroform or chloroform-ether mixture with the patient sitting up. Whichever method is employed, it will be advantageous to have some form of suction apparatus.

After the operation such patients should be suitably postured to permit of drainage of blood and mucus from

pharynx and mouth and to prevent the tongue from dropping back. It may help to leave a suture through the tongue or an artificial airway *in situ*.

Wounds of the Laryngo-Tracheal Region.

The initial surgical treatment for wounds in the region of larynx and trachea will be directed to ensuring that respiration is not obstructed. A low tracheotomy may be required, and for this local analgesia will be adequate. Subsequent surgical treatment may require a general anæsthetic, for which ether or chloroform, administered by the endotracheal method through the tracheotomy tube, may be used. For this type of case (provided severe shock is not evident) oxygen bubbled through chloroform in a Junker's apparatus is an excellent way of introducing the anæsthetic vapour into the trachea through the tracheotomy tube.

Wounds of the Thorax.

From the point of view of anæsthesia wounds of the thorax present important problems: (*a*) at the time of the initial surgical therapy, because of severe shock and the interference with lung ventilation which accompany such wounds; (*b*) at the time of subsequent surgical procedures so frequently necessary because of the existence of sepsis of the pleural cavity and its contents with more or less interference with lung ventilation.

In a wounded man with a large open sucking wound of the chest immediate surgical treatment is called for. With such a condition inspiration and expiration produce flapping movements of the mediastinum, with severe dyspnœa. The consequences are not limited to impeding lung ventilation, but in some cases may be responsible for the tearing of the mediastinal pleura with the production of bilateral pneumothorax and death. A flapping mediastinum also has profound effects on the circulation, which are probably partly mechanical and partly the result of trauma. The initial treatment (plugging or through-and-through suturing) for such wounds will be given at one of the dressing stations in the forward area. The facilities for anæsthesia will be very limited; ether or chloroform analgesia may be all that is available, or in some cases no anæsthesia may be available. Later, when the shock has been recovered from and further operation is performed after the patient's removal to a casualty clearing station, nitrous oxide and oxygen anæsthesia with ether supplement will probably be the anæsthetic used. It is unnecessary and in fact inadvisable to raise the intrapulmonary pressure; the lung is already collapsed and perhaps injured, and attempts to inflate it will not only hamper the surgeon but increase the damage to the pulmonary tissues.

In some cases regional analgesia (field block or paravertebral dorsal block) may be employed. This may be preceded by some form of premedication and supplemented with nitrous oxide and oxygen anæsthesia.

It is necessary for the surgeon to yield as much as he can to the anæsthetist; for it will be more beneficial for the patient to be kept off his good side as far as possible.

In abdomino-thoracic wounds, where the wound in the diaphragm needs suturing, a somewhat deeper level of anæsthesia has to be attained.

Finally, later on, in the general hospital, where such patients may have to have further surgical intervention for empyema *et cetera*, with or without inflammatory involvement of lung tissue, there is only one anæsthetic agent to employ, should it be available, namely, cyclopropane. For this type of case it should prove ideal.

Abdominal Wounds.

Wounds of the abdomen are usually accompanied by signs of shock and hæmorrhage. The greater the part played by hæmorrhage in the shock-hæmorrhage syndrome, the more valuable is blood transfusion. It may be wise to withhold blood transfusion till operation is ready to be started. As these patients frequently require a thorough search of the abdominal viscera, with considerable cleansing of the peritoneal cavity (blood and intestinal contents), adequate relaxation is imperative.

In a small percentage of cases muscular relaxation may be attained with nitrous oxide and oxygen anæsthesia *plus* infiltration of the abdominal wall with a local anæsthetic; but in the majority some ether supplement will be called for. Straining impedes the surgeon at every step of the operation, so it must be avoided. In the hands of an inexpert gas anæsthetist far less harm will result to the patient if open ether (carefully administered) is employed. Spinal analgesia in the presence of shock and hæmorrhage will determine a fatal issue.

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References.

(1) J. F. W. Silk: "The Administration of Anæsthetics in Home Military Hospitals", *Proceedings of the Royal Society of Medicine*, Volume XI, November 2, 1917, page 1.
(2) D. E. Lewis: "Practice of Surgery", Volume I, page 29.
(3) G. Marshall: "Anæsthetics at a Casualty Clearing Station", *Proceedings of the Royal Society of Medicine*, Volume X, February 2, 1917, page 17.
(4) J. M. Weddell: "The Treatment of Wounds in War", *The British Medical Journal*, April 15, 1939, page 785.
(5) R. Jarman: "Anæsthesia in War Time", *The British Medical Journal*, April 29, 1939, page 896.
(6) L. O'Shaughnessy and D. Slome: "Ætiology of Traumatic Shock", *The British Journal of Surgery*, Volume XXII, January, 1935, page 589, and footnote, page 616.
(7) N. L. M. Reader: "Prevention and Treatment of Shock", *The British Medical Journal*, May 20, 1939, page 1053.
(8) *La Conférence chirurgicale interalliée*: *Archives de médecine et de pharmacie militaires*, Volume LXX, 1918.
(9) D. Cordier: *"Le problème de l'anesthésie chez les blessés gazés"*, *L'anesthésie et l'analgésie*, Volume IV, 1938, page 429.
(10) W. Hecksteden: *"Experimentelle Beiträge über Anwendung der Evipan Natriumnarkose nach Vergiftung mit Grünkreuzkampfstoff"*, *Archiv für experimentelle Pathologie und Pharmakologie*, Volume CLXXXVI, 1937, page 451.
(11) G. Jefferson: "War Wounds of the Head", *The British Medical Journal*, August 12, 1939, page 347.

British Medical Association News.

SCIENTIFIC.

A MEETING of the Victorian Branch of the British Medical Association was held at Yallourn Hospital, Yallourn, at the invitation of the Gippsland Subdivision of the Branch, on October 14, 1939, DR. F. L. DAVIES in the chair, supported by DR. G. A. HAGENAUER, President of the Gippsland Subdivision.

The Use of Sulphanilamides in Bacterial Infections.

DR. G. A. PENINGTON read a paper entitled "The Use of Sulphanilamides in Bacterial Infections" (see page 113).

DR. J. M. ANDREW thanked Dr. Penington for his very informative address, which would serve to clarify the haze in the minds of many practitioners concerning treatment with drugs of the sulphanilamide type. In the hope that Dr. Penington could throw some light on the occurrences he would like to give a brief account of some of his own difficulties in the matter. He had used the method of treatment for a patient with a pneumococcal infection and had ceased two days after the temperature had fallen to normal; but the illness had been followed by fatal pneumococcal meningitis. In the case of another patient, who had had a motor car accident with bruising, he had opened the knee joint and the patient had had mild fever for some eighteen days. Dr. Andrew had thought that this was due to absorption of blood clot. He had used sulphonamide treatment from the inception and had stopped it five days after the temperature had become normal; but four days later septicæmia, with pharyngitis

and pneumonia, had occurred, and the patient had died in a state of acute heart failure. Dr. Andrew commented that he had the impression that cessation of the treatment had allowed the latent infections to become active and no response had followed the readministration of the drug.

He also referred to an anomaly in the treatment of gonorrhœa. On one day he had seen two patients, one of whom had come for treatment on the day following the onset; this patient had been cured within two weeks; the other patient had had the condition for six weeks and the administration of sulphonamide had not appeared to have any beneficial effect on the progress.

Dr. Penington, at the invitation of the President, replied to the point raised by Dr. Andrew. He suggested that the failure of response to treatment might have been due to granulocytopenia. If that condition occurred there was complete absence of response to any treatment. The bone marrow was quite unable to respond; therefore there was no reaction to infection. He added that it was not a big job to take a blood smear, to stain it with Leishman's stain and to observe the polymorphonuclear leucocytes in the film. Films should be prepared twice a week and the proportion of polymorphonuclear cells estimated. If they were decreasing in number the sulphonamide preparation should be discontinued and pentnucleotide treatment commenced; if the polymorphonuclear cells were really scarce transfusion of blood was indicated.

Speaking of gonorrhœa, Dr. Penington commented on the great variation in virulence. He advocated the use of specific sera and vaccines to increase the resistance of the subjects to the invading organisms, and added that "M & B 693" was, in his opinion, to be preferred to sulphanilamide. He said that the rapid response occurring in some cases might be an indication that the patient had overcome the infection; but rigorous tests should be carried out to exclude the possibility of latency of infection; expert passage of sounds and urethroscopy rather than injections of silver nitrate in solution should be used as tests of cure.

DR. C. E. WILLING asked for information about the prophylactic use of the drugs under discussion in complicated midwifery work. He spoke of the depression associated with "Uleron" treatment, and mentioned that anterior urethritis had been reported as a sequel to "Uleron" treatment.

Dr. Penington, in reply to Dr. Willing, said that prophylaxis with sulphanilamide had not been found to be desirable; it was associated with a risk of toxicity and with depression of polymorphonuclear leucocytes, the multiplication of which was a main source of defence against infection. He went on to say that as a rapid concentration was obtainable with "M & B 693", "Soluseptasine" and some other members of the group, sufficient could be got into the system quickly when it was suspected that local or general infection was in progress. He did not wish to imply that "Uleron" should not be used; polyneuritis occurred infrequently, but was a serious and prolonged complication when it happened. Hæmaturia and non-bacterial anterior urethritis were important irritant effects on the genito-urinary system which could arise from the use of any of the preparations.

DR. W. G. FARRELL asked for information about the treatment of polyneuritis associated with the use of "Uleron".

Dr. Penington suggested that injections of vitamin *B* preparations were advisable in addition to the oral use of those preparations.

DR. C. A. M. RENOU said that for ten months he had been using "M & B 693" in the treatment of acute gonorrhœa at the Alfred Hospital, and he could only describe the results as miraculous; he had not had any experience of the allied drugs. In 90% of the cases the original discharge had ceased within a day or two and the patients had been clinically cured in a week; they were not discharged at that stage, but were kept for a further six weeks to test the cure and to look for relapses; there had been only three or four relapses, and they had come within two or three weeks. He spoke also of the desirability of passing a sound to test the cure; posterior urethritis occurred rarely, and epididymitis and orchitis were occasionally encountered. Treatment with "M & B 693" was repeated once, and if it was not effective it was abandoned and the former methods of treatment were adopted. Dr. Renou preferred not to express an opinion about the value of "M & B 693" for prophylactic use in gonorrhœa.

DR. M. D. SILBERBERG thanked Dr. Penington for what he characterized as a most comprehensive contribution to the knowledge of the subject under discussion. Dr. Silberberg had used the preparations extensively in pneumonia; but on analysis the figures had been a little disappointing; they were not so encouraging as were the impressions he had formed. The drugs did not protect the patients against complications such as empyema. With reference to rheumatic infection, he remarked that prophylactic use would be important, especially against the risk of carditis or bacterial endocarditis; so far it had been advocated for use during the day preceding and the day following tonsillectomy or dental extractions in such cases, and there was some experimental basis for that action; he would like to hear Dr. Penington's views on that subject. Dr. Silberberg went on to say that he had seen some extraordinary results with the use of the drugs. He mentioned as an instance the apparent cure of ulcerative endocarditis. The patient had symptoms of grave sepsis; he had lost much weight and suffered from profuse diarrhœa, passing blood-stained stools; though the patient had been very ill and had appeared likely to die, he had recovered, had gained weight and had become very well. In another instance a striking result had been obtained in what was presumed to be bacterial endocarditis; but in other proven cases he was unable to report successful treatment.

Dr. Penington, in reply to Dr. Silberberg, said that in midwifery cases without any known focus of infection and without an opportunity to develop natural resistance, there was not any indication for the use of the drugs; but where the medical practitioner was dealing with foci such as septic tonsils or an abscess at the apex of a tooth, natural resistance could be aided by "M & B 693"; it was inimical to *Streptococcus viridans*, which was a normal and common causative organism in infective endocarditis. He referred to a report by Whitby of a case in which there had been a definite response to the drug in the way of lowering of temperature and clinical improvement, and that favourable response had been repeated; but after three weeks it had been thought inadvisable to continue, and later the patient had failed progressively to respond and the case had terminated fatally. Dr. Penington also drew attention to the fact that patients might recover from subacute bacterial endocarditis without "M & B 693", and he gave as an instance the case he had reported in THE MEDICAL JOURNAL OF AUSTRALIA (March 5, 1932, page 329); that patient was still quite well. Speaking of the precautions to be adopted, Dr. Penington mentioned that patients undergoing treatment should not expose themselves to strong sunlight; they should report to their medical attendant at least once a week; on the occurrence of any unusual symptom they should stop taking the drug and inform their medical attendant immediately; they should be warned that slight depression or headache usually disappeared on perseverance with the drug, and that it was of importance that they should acquire the ability to tolerate it during the early stages of the illness and of its use.

DR. H. F. MAUDSLEY thanked Dr. Penington for the clarification of the subject and for the clear exposition of the use of the drugs. Dr. Maudsley spoke of the way in which meningitis was cleared up with "M & B 693" combined with constantly repeated lumbar puncture. On the other hand, he had seen a patient with meningitis treated with the drug only, and the result had not been good. He asked Dr. Penington for information concerning reported neurological complications of the treatment. He mentioned two instances of encephalomyelitis associated with the use of sulphanilamide in *lupus erythematosis* and rheumatic fever respectively; the occurrence might be due

to idiosyncrasy or to previous infection; he had wondered whether they should look for such idiosyncrasy. He went on to say that at times the drug was used as a shot in the dark; a patient undergoing "Somnifaine" treatment developed bronchopneumonia, and empyema threatened; but "M & B 693" was given and the patient's condition cleared up extraordinarily quickly.

Dr. Penington, in reply to Dr. Maudsley, said that an author had advocated not draining the theca in meningitis; he himself thought that the performance of lumbar puncture was indicated, especially on account of the importance of the determination of the pressure of the cerebro-spinal fluid. He always used a manometer, the limit of which was 40 cubic centimetres of water pressure; one could be made simply of capillary tubing with a short rubber connexion. It was not satisfactory to gauge the pressure by the rate of the drops. By manometry an indication was obtainable as to how much fluid should be taken off and whether repetition was necessary. If the fluid tended to become thicker, cisternal puncture might be desirable for the relief of pressure. Dr. Penington also said that he had missed the reports of neurological complications to which Dr. Maudsley had referred; he understood that they had appeared very recently and, from the absence of earlier occurrences of a similar nature, he felt dubious as to whether the complications were really due to "M & B 693".

DR. A. E. COATES said that from surgical experience they were unable to assess the value of the drugs; the tendency to judge from incomplete data was to be deprecated, and yet it was not practicable to arrange adequate controls. Surgeons thought that drainage was essential where infections occurred and that no drugs could take the place of complete excision of infected material and proper drainage. He had had, however, some happy results with the drugs. He had performed a spinal operation and forty-eight hours later the patient had had a severe sore throat; and so had the medical man who had been present at the operation, and also a member of the family. The spinal wound had broken down and neck stiffness had developed, associated with ophthalmoplegia, inequality of the pupils, a rise of temperature to 105° F. and of pulse rate to 152 per minute. He had obtained pink pus from the *cisterna magna*, from which streptococci, meningococci and staphylococci had been grown. He had carried out a transfusion of blood and had initiated heavy "Proseptasine" treatment. The patient's temperature had fallen to 99° F. within four days, and the pulse rate had returned progressively to normal over a period of some five weeks. Only the one puncture had been required.

Dr. Coates commented that in cases such as the one he had described heroic measures were required in the presence of grave signs of toxæmia. He had seen other examples, such as streptococcal infection of the tendon sheaths of the hand, which by chemotherapy might be saved from operative treatment, though operation was necessary if pus formed.

DR. F. KINGSLEY NORRIS described Dr. Penington's paper as an extraordinarily valuable contribution. He had used "Proseptasine" soon after it had become available, and he had been impressed with the early results. A four-year-old child with *spina bifida occulta* had developed what was thought to be acute anterior poliomyelitis and had been admitted to the Infectious Diseases Hospital. On lumbar puncture the condition had been found to be cerebro-spinal meningitis. Redness had appeared over the *spina bifida*. "Proseptasine" had been given and the redness had subsided. Four weeks later the illness had flared up and subsided; but the red area had suppurated, symptoms of disturbance of the nerve supply to the lower extremities had appeared, and an extradural encysted abscess had formed. Dr. Norris said that he had used "Proseptasine" personally as a prophylactic against the common cold; he had chewed as many as thirteen tablets in twenty-four hours; it had caused him to do his work as if in a dream; he had felt as if he were floating in the air; but on three occasions he had succeeded in stopping the progress of a cold in the head. He sought information as to whether any sulphonamide was made locally or whether the outbreak of hostilities would affect the supply.

Dr. Penington, in reply to Dr. Norris, said that Drug Houses of Australia put up a satisfactory sulphonamide; but the tablets might be made from imported powder. He went on to say that people engaged in aviation should not continue in that avocation while undergoing treatment with that type of drug; it was dangerous to continue, as the judgement would be all astray; the same comment was applicable to surgeons, who should not perform operations while taking the drugs. He added that it had to be remembered that all colds in the head were not streptococcal infections. "Proseptasine" was certainly better tolerated than most of the preparations, and was specially indicated in streptococcal infections. If adequate dosage was required for the proper treatment of chronic infections the patients should be in bed and should not be allowed to go about carrying on their usual duties.

Correspondence.

THE HOLY NATIVITY: A BIOLOGICAL THEORY.

SIR: In view of the fact that archæology and geology have recently been effectively used to work out partial explanations of biblical miracles, it has occurred to me that the science of biology could be similarly applied to the miracle of the Holy Nativity to supply a partial explanation. To devise a biological theory one has only to assume that a female reproductive cell was the natural means used in this miracle, that is, that a female reproductive cell was supplied with energy or power, from an unusual or a supernatural source, to proceed directly with cell division and subdivision, using the whole of its own nucleus for this process, instead of obtaining the necessary energy by the usual method of extrusion of half of its own nucleus and its replacement by the half nucleus of a male reproductive cell.

Some confirmation of this theory is also to be found in the fact that in the animal and plant worlds asexual reproduction is not entirely unknown.

A biological theory of this type would be, in my opinion, preferable to some of the theological attempts that have been made at an explanation.

Yours, etc.,

JESSIE B. SIMPSON, M.B., B.S. (Melbourne).

"Rosehaugh",
35, Normanby Street,
Middle Brighton,
Victoria.
January 8, 1940.

THE DAWES FUND.

SIR: You were kind enough to publish in these columns an appeal made by us, on behalf of his widow and children, to old friends and associates of the late E. Dawes, senior laboratory assistant at the Royal Prince Alfred Hospital, and during the Great War, Australian Army Medical Corps corporal in the Fourth Battalion, and later sergeant, number 3 Australian General Hospital.

We wish to convey our thanks to the subscribers to this fund, and to inform them that the fund has now been closed and the sum total of £84 0s. 6d. has been paid to Mrs. Dawes. We have received her acknowledgement, and she desires to convey her sincerest thanks to all subscribers.

Yours, etc.,

A. H. TEBBUTT.
E. F. THOMSON.

143, Macquarie Street,
Sydney,
January 2, 1940.

Obituary.

ERNEST FRANCIS STANLEY SCANLON.

WE regret to announce the death of Dr. Ernest Francis Stanley Scanlon, which occurred on January 4, 1940, at Melbourne, Victoria.

CYRIL PHILLIPS BRYAN.

WE regret to announce the death of Dr. Cyril Phillips Bryan, which occurred on January 17, 1940, at Reno, Nevada, United States of America.

Nominations and Elections.

THE undermentioned have applied for election as members of the New South Wales Branch of the British Medical Association:

Ryan, Clement Maurice, M.B., B.S., 1939 (Univ. Sydney), Royal South Sydney Hospital, Zetland.
Walsh, Robert John, M.B., B.S., 1939 (Univ. Sydney), Sydney Hospital, Sydney.

The undermentioned have applied for election as members of the South Australian Branch of the British Medical Association:

Crompton, David Owen, M.B., B.S., 1939 (Univ. Adelaide), Adelaide Hospital, Adelaide.
Dawkins, Donal Campbell, M.B., B.S., 1939 (Univ. Adelaide), Adelaide Hospital, Adelaide.
Fenner, Frank John, M.B., B.S., 1938 (Univ. Adelaide), Adelaide Hospital, Adelaide.
Gold, Mervyn Roy, M.B., B.S., 1939 (Univ. Adelaide), Adelaide Hospital, Adelaide.
Stewart, John Samuel, M.B., B.S., 1939 (Univ. Adelaide), Adelaide Hospital, Adelaide.
Dunstone, Sydney Morgan Lewis, M.B., B.S., 1939 (Univ. Adelaide), Adelaide Hospital, Adelaide.

Diary for the Month.

FEB. 1.—South Australian Branch, B.M.A.: Council.
FEB. 6.—New South Wales Branch, B.M.A.: Organization and Science Committee.
FEB. 7.—Victorian Branch, B.M.A.: Branch.
FEB. 13.—New South Wales Branch, B.M.A.: Executive and Finance Committee.
FEB. 13.—Tasmanian Branch, B.M.A.: Branch.
FEB. 15.—Western Australian Branch, B.M.A.: Council.
FEB. 20.—New South Wales Branch, B.M.A.: Ethics Committee.
FEB. 23.—Tasmanian Branch, B.M.A.: Council.
FEB. 27.—New South Wales Branch, B.M.A.: Medical Politics Committee.
FEB. 28.—Victorian Branch, B.M.A.: Council.
FEB. 29.—South Australian Branch, B.M.A.: Branch.

Medical Appointments Vacant, etc.

For announcements of medical appointments vacant, assistants, *locum tenentes* sought, etc., see "Advertiser", pages xvi-xix.

CHILDREN'S HOSPITAL, CARLTON, VICTORIA: Clinical Assistant to Honorary Radiologist.
MCKINLAY HOSPITALS BOARD, JULIA CREEK, QUEENSLAND: Medical Officer.
ROYAL ALEXANDRA HOSPITAL FOR CHILDREN, SYDNEY, NEW SOUTH WALES: Honorary Officers.
SYDNEY HOSPITAL, SYDNEY, NEW SOUTH WALES: Temporary Honorary Relieving Assistant Orthopædic Surgeon.
THE UNIVERSITY OF MELBOURNE, VICTORIA: Part-Time Demonstrator in Clinical Bio-Chemistry.

Medical Appointments: Important Notice.

MEDICAL PRACTITIONERS are requested not to apply for any appointment referred to in the following table without having first communicated with the Honorary Secretary of the Branch named in the first column, or with the Medical Secretary of the British Medical Association, Tavistock Square, London, W.C.1.

BRANCHES.	APPOINTMENTS.
NEW SOUTH WALES: Honorary Secretary, 135, Macquarie Street, Sydney.	Australian Natives' Association. Ashfield and District United Friendly Societies' Dispensary. Balmain United Friendly Societies' Dispensary. Leichhardt and Petersham United Friendly Societies' Dispensary. Manchester Unity Medical and Dispensing Institute, Oxford Street, Sydney. North Sydney Friendly Societies' Dispensary Limited. People's Prudential Assurance Company Limited. Phœnix Mutual Provident Society.
VICTORIAN: Honorary Secretary, Medical Society Hall, East Melbourne.	Associated Medical Services Limited. All Institutes or Medical Dispensaries. Australian Prudential Association, Proprietary, Limited. Federated Mutual Medical Benefit Society. Mutual National Provident Club. National Provident Association. Hospital or other appointments outside Victoria.
QUEENSLAND: Honorary Secretary, B.M.A. House, 225, Wickham Terrace, Brisbane, B.17.	Brisbane Associate Friendly Societies' Medical Institute. Proserpine District Hospital. Members accepting LODGE appointments and those desiring to accept appointments to any COUNTRY HOSPITAL or position outside Australia are advised, in their own interests, to submit a copy of their Agreement to the Council before signing.
SOUTH AUSTRALIAN: Secretary, 178, North Terrace, Adelaide.	All Lodge appointments in South Australia. All Contract Practice Appointments in South Australia.
WESTERN AUSTRALIAN: Honorary Secretary, 205, Saint George's Terrace, Perth.	Wiluna Hospital. All Contract Practice Appointments in Western Australia.

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